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Editorial

Surgical Relief of Myocardial Ischemia

THE brilliant achievements of cardiac surgery in curing or ameliorating congenital and acquired defects have inspired increased efforts to augment the myocardial blood supply of patients suffering from advanced coronary atherosclerosis. Clinical improvement in patients with angina pectoris has been reported following various procedures such as omentopexy, aortic-coronary sinus anastomosis, coronary sinus ligation, myocardial implantation of the internal mammary artery and stimulation of pericardial adhesions by magnesium silicate, asbestos and other foreign substances.

All these operations have as their objective the introduction of an extracardiac blood supply which will substantially augment the deficient coronary flow. Protection against subsequent myocardial infarction might also be provided. These various procedures have been subjected to the test of animal experimentation, patients have been operated upon and favorable effects on angina pectoris have been observed. No method, however, has received widespread acceptance.

The criteria which such procedures should meet in the laboratory and in the clinic are severe.[1] Surgery is not indicated for the milder cases of angina pectoris since medical measures usually suffice to make a worth while and comfortable life possible. Those subjects selected for surgical treatment are seriously ill angina pectoris patients who cannot withstand even minor procedures without risk, hence the operation must be relatively simple. The immediate operative mortality of certain of the proposed procedures has been as much as 20 per cent.

Proof of the surgical augmentation of arterial blood supply to the myocardium has been beset with difficulties. Experimental studies utilizing the dog encounter a different coronary arterial tree from that of man.[2] Large anastomoses between the left anterior descending and left circumflex and right coronary occur rather frequently in the dog, thus rendering the effects of ligation of a single artery such as the left anterior descending in a series of experiments highly variable and difficult to interpret.

The attempted demonstration of a new functional blood supply in operated animals has been complicated by technical problems. It is not always realized that capillary intercoronary anastomoses exist normally and that similar communications not infrequently extend from the heart via the pericardial reflections to neighboring structures such as the aorta or pulmonary artery.[3] These communications can be readily demonstrated by the injection of watery solutions into a coronary artery after which the injected solution becomes immediately discernible elsewhere over the heart. These fine connections are of no immediate functional significance for they do not protect the myocardium from infarction if a coronary artery is suddenly occluded. Accordingly, demonstration after operations of such fine communications between the heart and surrounding structures by colored watery solutions or India ink is of little importance. To demonstrate functional collateral channels, either extra-cardiac or interarterial coronary anastomoses, more viscous

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[2] PIANETTO, M. B. The coronary arteries of the dog. *Am. Heart J.*, 18: 403, 1939.

[3] GREGG, D. E., THORNTON, J. J. and MAUTZ, F. R. The magnitude, adequacy and source of collateral blood flow and pressure in chronically occluded coronary arteries. *Am. J. Physiol.*, 127: 161, 1939.

injection masses which require larger channels should be used and the size of the vessels which such injection materials delineate should be determined. The Schlesinger lead-agar mass, for instance, does not penetrate generally to vessels less than 40 micra in diameter as found in fixed sections, which corresponds to 80 micra in fresh tissue.[4] Intercoronary anastomoses of this caliber exist in only 15 per cent of normal human hearts and are not abundant. In the presence of coronary narrowing or occlusions they are abundant and always present. The network is so rich, indeed, that it is difficult at times to conceive how it can be further increased by surgical means. Experimentally these anastomoses have been shown to obviate the dire effects of sudden complete occlusion.[5] The recent excellent studies of Eckstein, Leighninger and their associates[6] demonstrated that the stimulation of such a functional intercoronary collateral bed probably accounts for the long-term protection against coronary ligation in the normal dog heart rather than any direct increased arterial blood supply from the aortic-coronary sinus graft. There is no evidence that beneficial effects would result if the aortic-sinus graft were applied to a heart already the site of coronary arterial narrowings and occlusions. Similarly, Burchell[7] concluded from his meticulous studies on coronary occlusions in dogs that the role played by vascular channels in surgically produced pericardial adhesions in supplying blood to the myocardium was minimal or non-existent.

In brief, demonstration of the larger anastomatic channels produced as a consequence of the operative procedure has not received adequate attention. Nor are there any convincing blood flow studies which demonstrate that any therapeutic surgical operation leads to a sustained increase in arterial blood flow in a heart with prior coronary narrowings or occlusions. Caution must be observed in applying the results of experiments on the normal dog heart to the diseased atherosclerotic human heart with its established narrowings, occlusions and rich network of compensating intercoronary anastomoses.

The clinical evaluation of operative procedures designed to increase the myocardial blood supply is also beset with difficulties. The nerve pathways from the heart to the nerve roots are not clearly defined. They traverse a wide pathway[8] and may be interrupted by the operative procedure. Further studies are needed to evaluate this possible factor. Whether the survivors will have an augmented life span or a reduction in the number and size of infarcts will be almost impossible to determine because of the inherent unpredictability of the clinical course.

As in the instance of surgical correction of congenital defects and acquired valvular disease, our knowledge will be furthered by these valiant attempts to increase the myocardial blood supply. Studies of coronary blood flow and adequate pathologic examination of the resultant myocardial effects in the experimental animal and carefully controlled observation in patients subjected to this experimental approach are still needed before the general clinical application of any of these procedures is warranted.

HERRMAN L. BLUMGART, M.D.
and MILTON H. PAUL, M.D.

[4] SCHLESINGER, M. J. An injection plus dissection study of coronary artery occlusions and anastomoses. *Am. Heart J.*, 15: 528, 1938.

[5] BLUMGART, H. L., ZOLL, P. M., FREEDBERG, A. S. and GILLIGAN, D. R. The experimental production of intercoronary arterial anastomoses and their functional significance. *Circulation*, 1: 10, 1950.

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Clinical Studies

Use of ACTH in the Diagnosis of Adrenal Cortical Insufficiency*

DALTON JENKINS, M.D.,† PETER H. FORSHAM, M.D.,‡ JOHN C. LAIDLAW, M.D., WILLIAM J. REDDY, A.B. *and* GEORGE W. THORN, M.D.

Boston, Massachusetts

PRESENT concepts of pituitary-adrenal cortical function hold that adrenal cortical activation normally occurs only as a consequence of stimulation by the adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland. With the availability in 1946 of ACTH suitable for clinical use it soon became evident that the administration of this material to subjects with intact adrenal cortical function produced a wide spectrum of metabolic changes consistent with the enhancement of all known functions of the adrenal cortex.[1,2] The striking absence of these changes in patients with Addison's disease receiving ACTH led to the development of standardized procedures for the evaluation of adrenal cortical function in man.[3,4] This report summarizes the experience of seven years in the clinical use of the ACTH test in normal subjects, patients without adrenal cortical disease and in patients with adrenal cortical insufficiency.

MATERIALS

Some knowledge of the history of commercial preparations of ACTH is important in understanding the development of currently employed diagnostic procedures. Early commercial lots of the hormone were mainly derived from hog or sheep pituitaries by acetone extraction and isoelectric precipitation.[5,6] Dosage was originally expressed in milligrams. An international reference was later prepared (Armour, La-1-a): the activity of 1.0 mg. of this standard preparation in Sayers' assay[7] (adrenal ascorbic acid depletion resulting from the intravenous injection of ACTH in hypophysectomized rats) was designated as 1.0 U.S.P. or International unit. Despite considerable variation in solubility and content of non-specific protein these early batches of ACTH were surprisingly effective.

In 1950 serious discrepancies were noted between labeled potency and clinical activity. Investigation of this phenomenon (probably attributable to modifications in preparative methods imposed by the demands of mass production) revealed that certain preparations of ACTH were subject to a marked degree of inactivation when administered by the intramuscular route.[8] On the other hand, intravenous administration of these preparations elicited the anticipated adrenal response. Indeed, a prolonged, continuous intravenous infusion of relatively small quantities of ACTH produced intensive adrenal cortical activation.[9] The administration of ACTH by continuous intravenous infusion was therefore exploited as a highly reliable procedure for the measurement of adrenal cortical reserve.[10,11]

About this time, Astwood and his collaborators[12] achieved a major advance in the methodology of ACTH preparation, employing glacial acetic acid extraction of hog pituitaries followed by adsorption on oxycellulose columns and differential elution. The therapeutic effectiveness of these highly purified preparations (activity up to 100 U.S.P. units per mg. or greater) when given intramuscularly proved to be two to four times greater than that of the

* From the Department of Medicine, Harvard Medical School, and the Medical Clinic, Peter Bent Brigham Hospital, Boston, Mass. These studies were supported in part by grants from the National Institutes of Health, United States Public Health Service; the Armour Laboratories, the Upjohn Company and the John H. Harris Fund.

† Present address: University of Colorado School of Medicine, Denver, Colo.

‡ Present address: University of California School of Medicine, San Francisco, Calif.

cruder products.[13] However, both types of corticotrophin were of equal potency when given by intravenous infusion indicating that the apparent "potentiation" of the purified hormone actually resulted from a significant decrease in extravascular inactivation.[14] Fortunately, the most widely employed preparations available at the present time lose only 10 to 20 per cent of their activity following intramuscular injection as compared to intravenous administration.

Finally, the development of efficient, slowly absorbed gelatin vehicles has resulted in the production of long-acting preparations of purified ACTH for intramuscular or subcutaneous administration. Because of their enhanced activity, due to the use of highly purified ACTH as well as to the prolongation of hormone action, certain difficulties in standardization of ACTH-gels have arisen.[15] Consequently, these products have been arbitrarily restandardized in terms of "commercial" or "clinical" units in a ratio of three (clinical) to one (U.S.P.). Thus in order to produce a clinical effect approximately equivalent to that induced by the intermittent intramuscular injection of 40 U.S.P. units of the older lyophilized preparations, a single injection of approximately 13 to 14 U.S.P. units of a highly purified ACTH in gelatin is required. However, the latter product is actually labeled as 40 "commercial units" or as "clinically equivalent to 40 U.S.P. units." In short, the gel preparations are "standardized" in terms of the clinical effect produced rather than in terms of the actual number of U.S.P. units of ACTH contained. Clinical experience with these preparations has thus far been very satisfactory. An intramuscular injection of 60 to 80 clinical or commercial units of ACTH in gelatin produces adrenocortical stimulation approximately equivalent to that elicited by an intravenous infusion of 20 U.S.P. units of lyophilized ACTH over an eight-hour period, as measured by the twenty-four-hour output of adrenocortical steroids. Because of their convenience, it is apparent that these highly effective long-acting preparations should achieve extensive diagnostic and therapeutic use.

METHODS

All studies were carried out in the metabolic unit and medical wards of the Peter Bent Brigham Hospital. The diagnoses of primary (Addison's disease) and secondary (hypopituitarism) adrenal cortical insufficiency were established by criteria previously described in detail.[16] The majority of these patients have been followed for many years and have undergone repeated diagnostic and therapeutic studies. Sixteen per cent of the control group were normal adult subjects; the remaining 84 per cent were hospital or clinic patients with a wide variety of medical disorders not specifically involving the pituitary-adrenal system. It is emphasized that the choice of a heterogeneous control group was deliberate since, in actual practice, the differential diagnosis of adrenal insufficiency entails the study of patients rather than normal individuals. Indeed, many of the patients included in the control group had been referred to this clinic for diagnostic evaluation of adrenal cortical function.

The reliability of the ACTH test obviously depends upon the validity of the criteria of adrenal stimulation. Two criteria were used in these studies: (1) an indirect index—a decrease in circulating eosinophils, selected because of the rapidity and convenience of the measurement; and (2) a direct index—a rise in the urinary excretion of adrenal steroids, selected because of a high degree of specificity of this response to adrenal cortical activation.

A variety of methods are now available for the direct enumeration of circulating eosinophils. Initially, the eosin-acetone stain of Dunger[17] and a modification of the eosin-propylene glycol stain of Randolph[18] were used. Recently, Hinkleman's stain[19] has also been employed. Factors involved in the accuracy of direct eosinophil counts have been discussed by others.[19,20] Of particular importance to proper interpretation of the eosinopenic response to ACTH are: (1) the numerical level of the initial eosinophil count and (2) the number of chambers counted. Table 1 shows the effects of these variables as determined in this laboratory.[21] The 95 per cent confidence limits are essentially the same as those determined by Best et al.[20] It is evident that the precision of the counting procedure itself varies directly with the number of eosinophils counted. Further, the significance of the eosinopenia elicited following ACTH increases markedly with higher initial counts. No patients with eosinophil levels below 100 cells per cu. mm. have been included in this study.

Urinary 17-ketosteroids were measured by a modification of the Holtorff-Koch[22] procedure. Urinary "17-hydroxycorticoids" (17, 21-dihydroxy-20-ketosteroids) were determined by a

previously described method[23] for the estimation of total corticosteroids hydroxylated at position C-17 (e.g., hydrocortisone, cortisone, tetrahydrocortisone). This procedure involves extraction of urine with n-butanol and subsequent application of the phenylhydrazine-sulfuric acid

TABLE I
INTRINSIC ERROR OF DIRECT EOSINOPHIL COUNTS

Initial Eosinophil Count (per cu. mm.)	No. of Chambers Counted	Eosinopenia is Significant* If Greater Than: (%)
300	8	15
	4	20
	2	30
150	8	20
	4	30
	2	40
100	8	25
	4	35
	2	45
50	8	35
	4	45
	2	60

* P less than 0.05.

Direct eosinophil counts possess a minimal inherent error due to chance variations in distribution cells and in the irreducible variations of technic. In comparing two eosinophil counts it must be remembered that variations in counts occur purely on the basis of chance. As the table shows, significance decreases considerably with small initial counts and with a small number of fields counted. (Based on data of Drs. F. G. Goetz and J. Worcester.[21])

colorimetric reaction of Porter and Silber.[24] The original method has been modified by one of the authors (W. R.)[25] as follows:

A 10 cc. aliquot of urine is adjusted to pH 1.0 (indicator paper) with 50 per cent sulfuric acid and then saturated with anhydrous sodium sulfate. A single extraction with 10 cc. of purified butanol* is carried out in glass-stoppered bottles or tubes by mechanical shaking for five minutes. After centrifuging (2,500 r.p.m.) for five minutes, 5 cc. of the supernatant butanol layer is carefully pipetted off. To this, 0.5 gm. of anhydrous sodium carbonate is added, shaken vigorously for one minute, allowed to stand for five minutes, and then centrifuged for five minutes. The butanol is again decanted off into a clean tube and colorimetry is carried out:

A Tubes	B Tubes
4 cc. of phenylhydrazine-sulfuric acid reagent (65 mg. phenylhydrazine hydrochloride in 100 cc. of 62 per cent sulfuric acid) is added to:	4 cc. of 62 per cent sulfuric acid is added to:
1 cc. butanol extract (sample A)	1 cc. butanol extract (sample B)
1 cc. butanol (blank A)	1 cc. butanol (blank B)
1 cc. cortisone standard	1 cc. cortisone standard

(The cortisone standard contains 20 μg. of free cortisone per cc. of purified butanol.)

The tubes are thoroughly mixed and incubated in a constant temperature water bath at 60°c. for exactly twenty minutes and then transferred to a cold water bath for five minutes. The optical density is read at 410 millimicrons on a spectrophotometer set at zero with a distilled water blank. Then:

Sample A − Sample B = (*a*)
Blank A − Blank B = (*b*)
(*a*) − (*b*) = corrected optical density of the unknown sample.

The corrected optical density of the standard is derived in the same manner and calculations are then carried out in the usual way.

Normal values range from 1.0 to 10.0 mg. per twenty-four hours, with a mean of 5.2 mg. per twenty-four hours. The advantages of the procedure are its comparative simplicity and a close

* Commercial butanols contain varying quantities of non-specific chromogens which may seriously interfere with the colorimetric reaction. These may be significantly reduced by the following procedure, suggested by Longwell:[26] Butanol is mixed with 0.1 volume of the phenylhydrazine-sulfuric acid reagent employed in the final colorimetric reaction (as mentioned previously) and allowed to stand at room temperature for five to seven days. The mixture is then washed once with an equal volume of distilled water, the butanol decanted off, dried over anhydrous sodium sulfate and distilled through a fractionating column. That fraction which comes over at 117°c. is collected, treated with anhydrous sodium carbonate (approximately 30 gm. per L.), allowed to stand overnight and then redistilled. The optical density of the final product, read against distilled water in a one-centimeter cuvette on a Coleman Junior spectrophotometer, should be less than 0.025.

correlation with the known state of adrenal cortical secretory function.[23] One of the authors (P. H. F.) has had an extensive experience with a modification of this procedure in which the final butanol extract is evaporated to dryness, taken up in methanol and the phenylhydrazine-sulfuric acid colorimetric reaction applied. Smith et al.[27] have described a further modification in which higher values are obtained, largely due to the use of a lower concentration of sulfuric acid in the colorimetry. Satisfactory results have been obtained by Jailer[28] applying the Porter-Silber reaction to chloroform extracts of urine previously subjected to beta-glucuronidase hydrolysis. Glenn and Nelson[29] have recently described a somewhat more complex but effective procedure utilizing chloroform extraction of urine following glucuronidase hydrolysis, purification of the extracts by column chromatography and application of the phenylhydrazine-sulfuric acid reaction to the eluate. These procedures or suitable modifications probably will be widely used in clinical laboratories for the measurement of urinary corticosteroids.

TABLE II
RAPID ACTH TEST

Subjects	No. of Tests (n)	Change in Eosinophils (%)			
		Mean (m)	Range	Standard Deviation (s)	Standard Error (e_m)
Controls (411)	442	−63	0 to 100*	±20.7	±1.0
Addison's disease (65)	103	− 7	+72 to −69†	±20.2	±2.0

* Eosinopenia less than 50 per cent in 104 cases (24 per cent).
† Eosinopenia greater than 50 per cent in 1 case (1 per cent).

Standard Deviation:

$$s = \pm\sqrt{\frac{S(x - m)^2}{(n - 1)}}$$

Standard Error of Mean:

$$e_m = \pm\frac{s}{\sqrt{n}}$$

RESULTS

Rapid ACTH Test. This is a screening test based upon the fall in circulating eosinophils normally produced by a single intramuscular injection of ACTH: An initial eosinophil count was performed and 25 U.S.P. units of ACTH (lyophilized) injected intramuscularly. Four hours later a second eosinophil count was obtained and the percentile fall in circulating eosinophils calculated. An eosinopenia of 50 per cent or more is considered normal.

The results of 545 tests in 476 patients are summarized in Table II. A mean eosinopenia of 63 per cent was obtained in normal subjects and patients with intact adrenal cortical function, whereas the mean fall in patients with Addison's disease was only 7 per cent. As shown in Figure 1, the fiducial limits of these means are well separated. However, the individual responses were widely distributed in both the control group (range: 0 to 100 per cent; standard deviation: ±20.7) and in patients with primary adrenal insufficiency (range: +72 to −69 per cent; standard deviation: ±20.2). Thus the 95 per cent confidence limits of the two groups show an extensive overlap. Moreover, a decrease in circulating eosinophils less than the arbitrarily designated norm of 50 per cent was observed in 104 cases (24 per cent) of the control group.

Twenty-four tests have been performed in eighteen patients with adrenal cortical insufficiency secondary to hypopituitarism. A mean eosinophil fall of 24 per cent was obtained (range: +59 to −75 per cent). In four cases (16 per cent) the eosinopenia exceeded 50 per cent. It would appear that the response of these patients to a single dose of ACTH depends upon the degree of secondary adrenal cortical atrophy present.

During the course of these studies a large number of commercial lots of ACTH, produced by a variety of manufacturers, has been used. In some instances a striking discrepancy between the adrenal responses produced by the intramuscular and intravenous administration of a given hormone preparation indicated that excessive extravascular inactivation had occurred. That this phenomenon was, at least in part, responsible for the inadequate response of many control subjects is suggested by examining the eosinopenic responses obtained with recently available, highly purified lots of ACTH of known potency. (Fig. 2.) The mean eosinophil falls of 10 per cent (fifteen patients with Addison's disease) and 73 per cent (thirty-five control patients) are adequately separated. More important, however, is a minimal overlap of the 95 per cent confidence limits, due primarily to a decreased scatter of the individual responses of control subjects. Two patients in the latter group exhibited an eosinopenia of less than 50 per cent. These results are directly comparable with those observed with the early, comparatively crude but effective preparations of ACTH used in this laboratory[17,30] prior to the development of mass-production methods of ACTH preparation. Nevertheless, the rapid test has been largely superseded in this laboratory by the procedures described below.

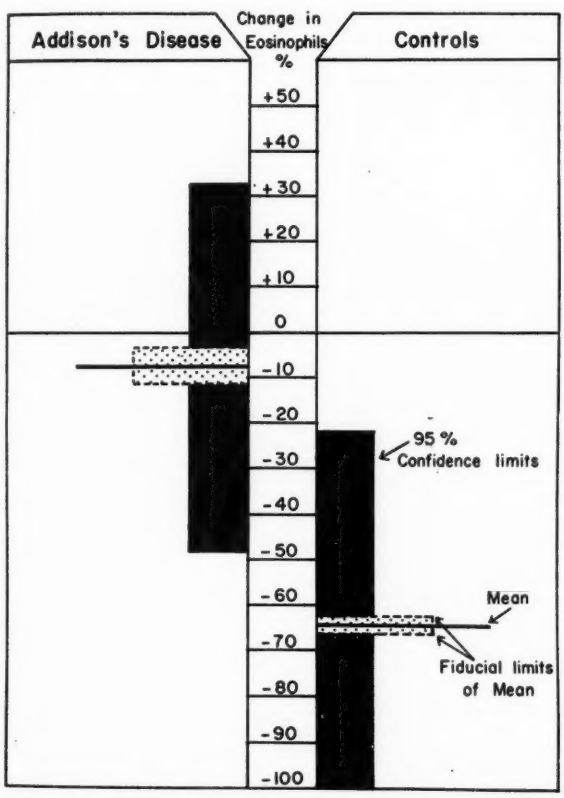

FIG. 1. The rapid ACTH test. The mean eosinopenic response of each group is indicated by the horizontal bar. The heavily shaded areas delimit the 95 per cent confidence limits of response [(mean eosinophil fall plus-or-minus two standard deviations). The stippled areas show the 95 per cent fiducial limits of the mean (the limits within which there is a 95 per cent probability that the true mean will lie: mean $\pm$ (t) (e_m)]. The figure is based on the data shown in Table II: 442 tests in control subjects and 103 tests in patients with Addison's disease.

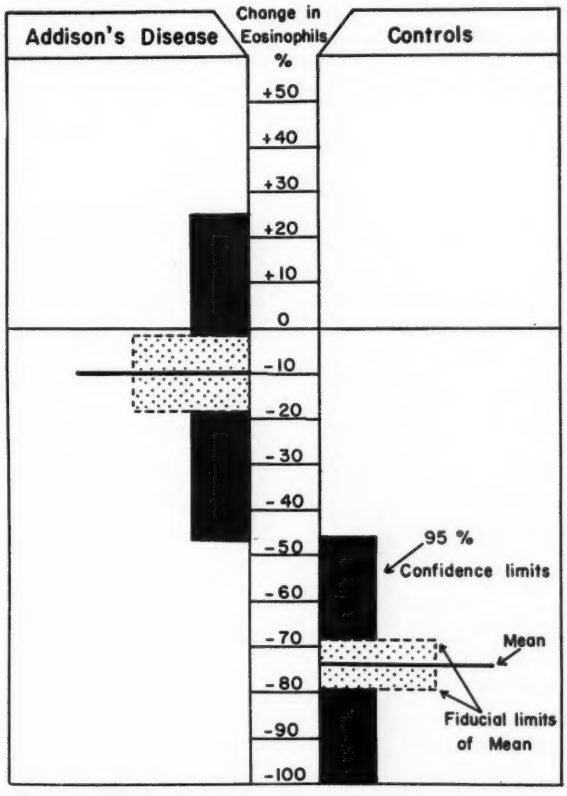

FIG. 2. Rapid ACTH test, using a highly purified preparation of ACTH. In contrast to Figure 1, there is minimal overlapping of the 95 per cent confidence limits of the two groups. (The increased spread of the 95 per cent fiducial limits of the means is largely attributable to the smaller groups represented in this figure.) Based on thirty-five tests in control subjects and fifteen tests in patients with Addison's disease.

Definitive ACTH Tests. Accurate measurement of the adrenal cortical reserve is greatly facilitated by imposing a stimulus of maximal or near-maximal intensity. Quantitative studies[11] have demonstrated that the degree of adrenal cortical activation produced by ACTH is directly proportional to the duration of the stimulus. Two procedures have been employed to provide prolonged and intensive stimulation:

(1) a continuous intravenous infusion of ACTH and (2) an intramuscular injection of highly purified ACTH in a slowly absorbed gelatin vehicle. For comparative study, both circulating eosinophils and urinary steroid excretion have been used as indices of adrenal activation.

the 95 per cent confidence limits of response in the two groups are clearly separated. (Fig. 3.) This signifies, even more than the wide separation of the fiducial limits of the means, a high degree of reliability in individual subjects. In only one instance was a distinctly subnormal

TABLE III
INTRAVENOUS ACTH TEST

Index	Controls			Addison's Disease		
	Eosinophils (% change)	17-Ketosteroids (mg. change per 24 hr.)	17-Hydroxycorticoids (mg. change per 24 hr.)	Eosinophils (% change)	17-Ketosteroids (mg. change per 24 hr.)	17-Hydroxycorticoids (mg. change per 24 hr.)
Mean	−94	+5.2	+15.2	−1	+0.3	+0.1
Range	−34 to −100*	0 to +19†	+4.5 to +30.6‡	+77 to −71§	−2.9 to +2.8	−1.2 to +1.9
Standard deviation	±8.2	±2.9	±6.2	±27.5	±0.4	±0.8
Standard error	±0.7	±0.2	±0.9	±4.2	±0.1	±0.5
No. of patients	141	137	52	37	37	10
No. of tests	152	151	52	42	41	10

* Eosinopenia less than 75 per cent in one case.
† 17-ketosteroid rise less than 2.0 mg. in nineteen cases (14 per cent).
‡ 17-hydroxycorticoid rise less than 5.0 mg. in two cases (5 per cent).
§ Eosinopenia greater than 50 per cent in one case (2 per cent).

Intravenous ACTH. On the first day a twenty-four-hour collection of urine was made for control 17-ketosteroid and 17-hydroxycorticoid determinations. On the following day 20 to 25 U.S.P. units of ACTH (lyophilized), dissolved in 500 cc. of normal saline solution or 5 per cent dextrose in water, was administered by continuous intravenous infusion over a period of eight hours. Direct eosinophil counts were performed immediately prior to and at the termination of the infusion, and a second twenty-four-hour urine (including the period of infusion) collected for steroid measurements. Results are expressed as per cent change in circulating eosinophils and the absolute change (mg. per twenty-four hours) in urinary steroid excretion.

A mean eosinopenia of 94 per cent was produced in the control group, in striking contrast to a mean eosinophil fall of 1 per cent in patients with Addison's disease. (Table III.) Furthermore, eosinophil fall (−34 per cent) encountered in a control patient (diagnosis: psychoneurosis, anxiety state). Simultaneously, the patient failed to exhibit a significant rise in urinary 17-ketosteroid excretion; unfortunately, no 17-hydroxycorticoid measurements were carried out. Additional diagnostic studies failed to reveal any evidence of adrenal cortical insufficiency and subsequent re-testing with intravenous ACTH resulted in an essentially normal response. The reason for the initial abnormal test is not clear.

Control subjects showed a mean rise in 17-ketosteroid excretion of 5.2 mg. per twenty-four hours. However, the range of individual responses was wide (0 to 19 mg. per twenty-four hours) and in 14 per cent of the group (nineteen cases) the increase was less than 2.0 mg. per twenty-four hours. While the changes obtained in patients with Addison's disease were insignificant, it is obvious that the 95 per cent confidence

limits of the two groups completely overlap. (Fig. 4.)

The measurement of 17-hydroxycorticoid excretion has provided a far better index of adrenal cortical activation than the 17-ketosteroid response. A mean rise in corticoid output of 15.2 mg. per twenty-four hours has been obtained in fifty-two control subjects. Although the range of response (4.5 to 30.6 mg. per day) is wide, fifty-one cases (98 per cent) exhibited an increase of greater than 5.0 mg. per twenty-four hours. No significant changes have been encountered in a small group of patients with Addison's disease and the 95 per cent confidence limits of response in the two groups do not overlap. (Fig. 5.)

The data presented here have been confined to the results of a single day of ACTH infusion. While this procedure ordinarily is adequate for diagnostic use, a period of several days will further accentuate the differences in response of the two groups. Experience has shown that following three or more days of intravenous ACTH infusions control subjects invariably exhibit a significant rise in 17-ketosteroid excretion and urinary 17-hydroxycorticoid values may reach extremely high levels whereas patients with Addison's disease consistently fail to respond. Repeated stimulation may also be useful in evaluating adrenal reserve in patients with hypopituitarism and secondary adrenal cortical insufficiency. When adrenal cortical atrophy is marked, a single ACTH infusion may elicit a distinctly subnormal response; but repeated infusions on successive days characteristically produce a progressive increase in the degree of eosinophil fall and steroid excretion. (Fig. 6.)

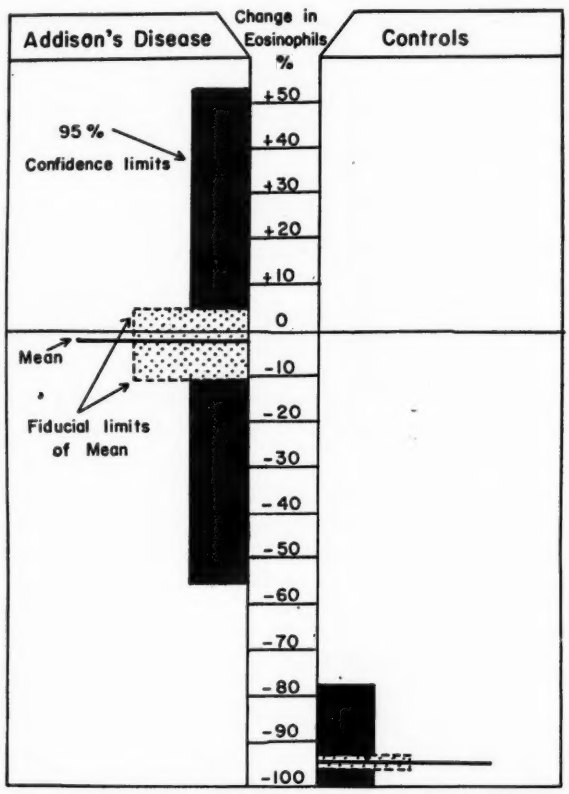

FIG. 3. Intravenous ACTH test: eosinophil response. The clear-cut separation of the 95 per cent confidence limits of the two groups emphasizes the high probability of an accurate evaluation of adrenal cortical reserve in individual subjects. Based on data shown in Table III: 152 tests in control subjects and forty-two tests in patients with Addison's disease.

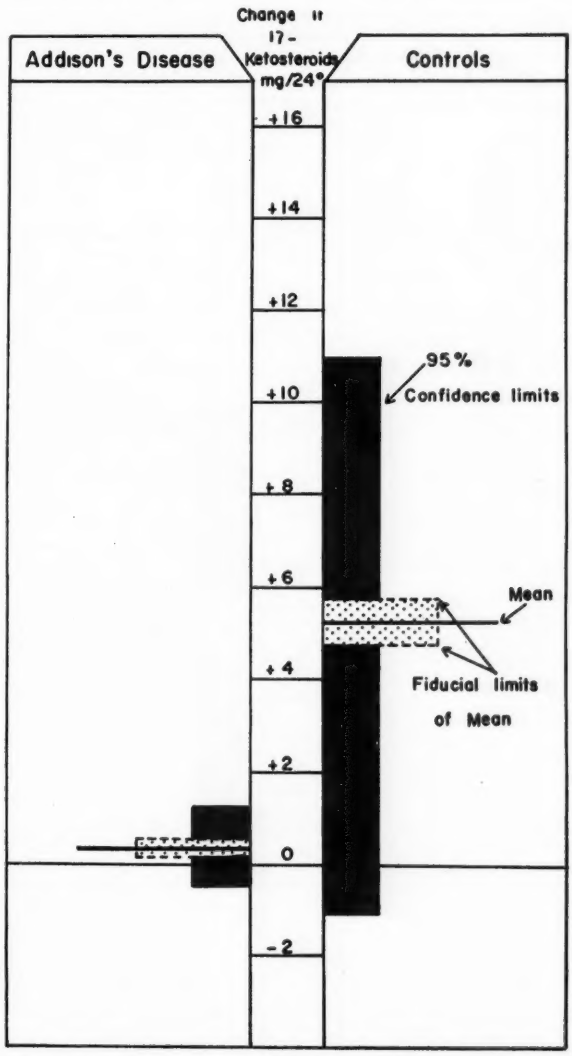

FIG. 4. Intravenous ACTH test: 17-ketosteroid response. Based on data of Table III: 151 tests in control subjects and forty-one tests in patients with Addison's disease.

In some cases several days of ACTH administration may be required to evoke a response equivalent to that of a normal individual receiving a single infusion.

Intramuscular ACTH-Gel. Twenty-four hour specimens of urine were collected for steroid

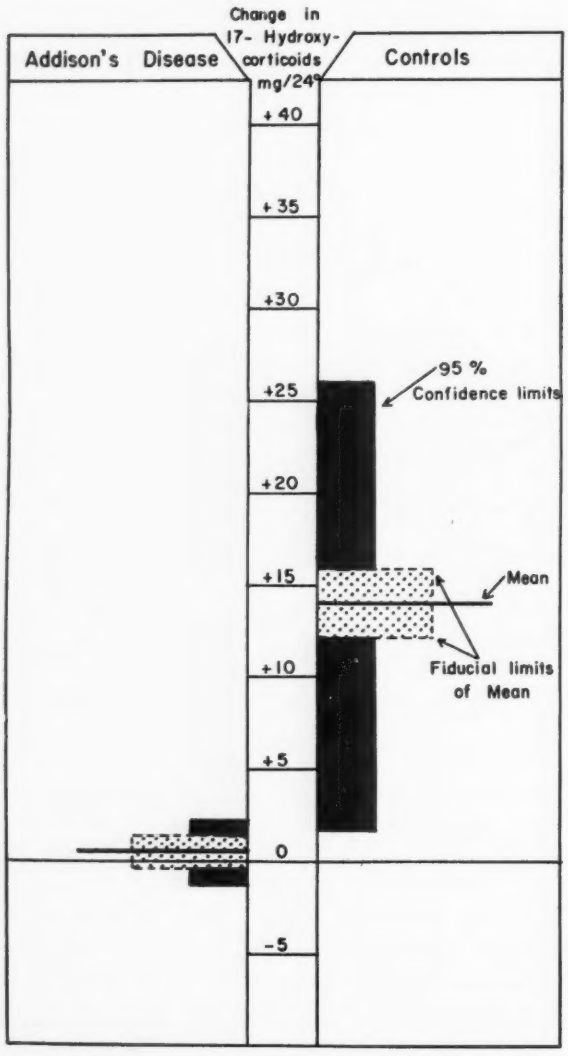

FIG. 5. Intravenous ACTH test: 17-hydroxycorticoid response. In contrast to the 17-ketosteroid response (Fig. 4), there is minimal overlapping of the 95 per cent confidence limits of response in the two groups. In addition, the greater absolute rise in steroid values contributes to a more accurate differentiation between the two groups. Based on data of Table III: fifty-two tests in control subjects and ten tests in patients with Addison's disease.

measurements on two successive days (as described for intravenous ACTH). On the second day two injections of 40 "commercial" or "clinical" units of a highly purified ACTH in gelatin were given at twelve-hour intervals. Circulating eosinophils were counted prior to the first dose of ACTH and eight to twelve hours later.

Data are available for only a limited number of studies. (Table IV.) The results shown are distinctly comparable with those obtained with an eight-hour intravenous infusion of ACTH. The eosinophil and 17-hydroxycorticoid responses are again satisfactory since the 95 per cent confidence limits of response for the two groups of subjects do not overlap. These preliminary studies indicate that the diagnostic use of purified ACTH in gelatin should afford adequate differentiation between patients with normal adrenal cortical reserve and patients with adrenal insufficiency.

COMMENT

The rapid (four-hour) ACTH test has been widely used as a screening procedure for the evaluation of adrenal cortical function. For a proper interpretation of results it is essential that the potential sources of technical error as well as the limits of accuracy of presently used methods for the direct enumeration of circulating eosinophils be understood. It is particularly emphasized that the use of this test in individuals with low initial eosniophil counts (e.g., less than 100 cells per cu. mm.) is hazardous due to the high error of the counting procedure under these circumstances.

It is important that the ACTH preparation employed be potent and capable of withstanding excessive extravascular inactivation. Results obtained with highly purified products, now available commercially, indicate that in many cases a reliable estimate of adrenal cortical function can be obtained by this procedure. Nevertheless, it is evident from the data here presented that the brief adrenal cortical stimulus provided by the rapid test is not of sufficient intensity to constitute a really definitive test of adrenal reserve. While the occurrence of marked eosinopenia makes adrenal cortical insufficiency unlikely, an eosinophil fall of less than 50 per cent cannot be accepted as diagnostic of adrenal cortical insufficiency. Indeed, the rapid test should never be employed as the sole diagnostic criterion of adrenal cortical function.

It is quite apparent that the prolonged and intensive stimulation produced by an eight-hour intravenous infusion of ACTH provides a more satisfactory test of adrenal cortical function. The pronounced fall in circulating eosinophils obtained with this procedure afforded a clearcut

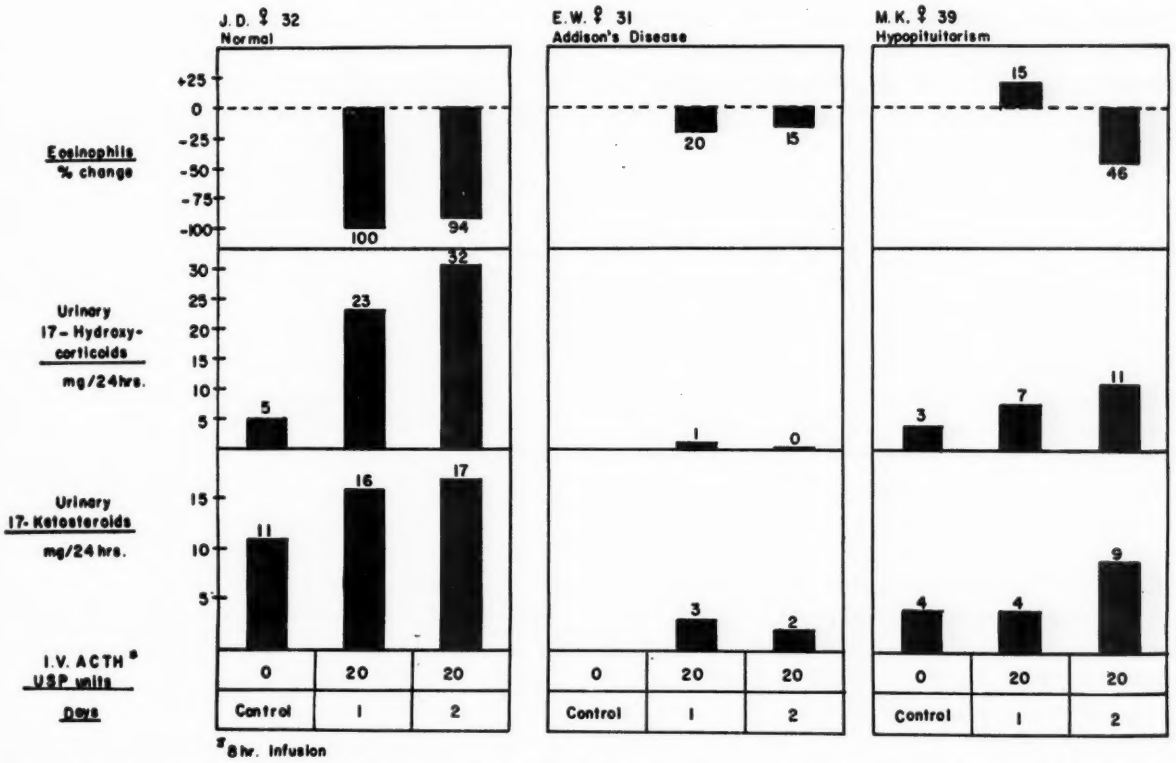

FIG. 6. Intravenous ACTH test. Representative eosinophil and urinary steroid responses of a normal subject, a patient with Addison's disease and a patient with panhypopituitarism to two successive eight-hour intravenous infusions of ACTH. The striking difference between the responses of the normal subject and the patients with adrenal cortical insufficiency is well demonstrated. Furthermore, comparison of the second day of ACTH infusion successfully differentiates, in this instance, primary from secondary adrenal failure.

TABLE IV

ACTH-GEL TEST

Index	Controls			Addison's Disease		
	Eosinophils (% change 8–12 hr.)	17-Keto-steroids (mg. change per 24 hr.)	17-Hydroxy-corticoids (mg. change per 24 hr.)	Eosinophils (% change 8–12 hr.)	17-Keto-steroids (mg. change per 24 hr.)	17-Hydroxy-corticoids (mg. change per 24 hr.)
Mean	−88	+6.1	+19.6	+28	−0.3	+0.1
Range	−66 to −100	0 to +19	+4.9 to +34.4	+1 to +55	−2.2 to +2.4	−1.6 to +1.3
Standard deviation	±10	±4.8	±10.3	±23.5	±1.5	±0.8
Standard error	±4	±1.2	±2.6	±8.7	±0.5	±0.3
No. of patients	12	17	18	7	10	10
No. of tests	12	17	18	7	10	10

differentiation between patients with primary adrenal cortical insufficiency and patients in the control group. While it is now quite clear that a fall in eosinophils may occur in the absence of an actual increase in adrenal cortical secretion (e.g., following epinephrine administration, or after certain types of exogenous stress of moderate intensity), it appears justifiable to conclude that a marked decrease in eosinophils *following intensive stimulation with ACTH* provides a reliable index of adrenal cortical activation.[31] However, the fact remains that change in eosinophil level is only an indirect measure of adrenal stimulation. The validity of the test is therefore greatly strengthened by demonstrating an increase in urinary steroid excretion. A rise in urinary 17-hydroxycorticoid output (5 mg. per twenty-four hours or greater) has proved to be a highly reliable and specific indication of the capacity of the adrenal cortex to respond to ACTH. Furthermore, the chemical procedure, in comparison to other methods for the estimation of urinary corticosteroids, offers the advantage of relative simplicity. In the opinion of the authors the measurement of 17-hydroxycorticoids is the index of choice in evaluating adrenal cortical stimulation. Blood levels of 17-hydroxycorticosteroids can also be measured[32] and have been successfully used in the calibration of adrenal cortical reserve.[33] This procedure has the desirable advantages for the patient of speed (a significant rise in blood levels ordinarily occurs within one hour) and of avoiding the inconvenience of urine collections. The chemical method itself, however, is technically somewhat more complex than that described for urine. An increase in urinary 17-ketosteroid output following ACTH infusion is also a direct but considerably less sensitive measure of adrenal cortical function.

Adverse reactions to the intravenous administration of ACTH are fortunately rare, especially when highly purified preparations of the hormone are used. In the course of several thousand intravenous infusions of ACTH in this clinic, six potentially serious reactions have been encountered, all in patients with adrenal cortical insufficiency (five patients with Addison's disease and one patient with adrenal cortical suppression due to prolonged nonspecific cortisone therapy). Apparently a normal increase in corticosteroid secretion offers considerable protection against a sensitivity reaction to the hormone. Two types of reaction have occurred: an *immediate* anaphylactoid response with pruritus, urticaria and occasionally wheezing, effectively controlled by epinephrine and antihistaminic agents; and a *delayed* reaction beginning several hours after the start of the infusion, characterized by fever and malaise and requiring symptomatic analgesic and antipyretic therapy. Should either type of reaction occur in patients with adrenal cortical insufficiency, it is imperative that cortisone or hydrocortisone be administered immediately in order to avert an adrenal crisis.

It appears from the preliminary data presented that reliable diagnostic studies can be obtained by the intramuscular injection of highly purified ACTH in gelatin. These preparations undergo comparatively little extravascular inactivation and produce prolonged activation of adrenal cortical secretion. It is therefore not surprising that the results obtained are directly comparable with those observed with intravenous infusion of the hormone. Since the necessity of prolonged intravenous infusion is avoided, an adequate test may be performed on an out-patient basis by this procedure. Furthermore, comparative studies have shown that a single intramuscular dose of 60 to 80 clinical units of ACTH-gel also produces an adequate eight- to twelve-hour eosinophil fall and a striking rise in urinary 17-hydroxycorticoid excretion. At this dosage level, or with 40 clinical units injected twice daily, continuation of the test for a period of several days is likely to provide a particularly clearcut differential response since the effects of the long-acting preparations become practically continuous. Because minute amounts of pitressin may be present in even the most highly purified preparations of ACTH, the trial should ordinarily not exceed three days in order to avoid excessive water retention; this is of especial importance in patients with adrenal insufficiency who tolerate water accumulation poorly. Patients who have previously become "resistant" to intramuscularly administered ACTH (excessive extravascular inactivation) may well show an inadequate response and should be tested by the intravenous procedure. It is not anticipated, on the basis of present experience, that this will be a frequent occurrence with the highly purified ACTH products now available.

The definitive tests were designed primarily for diagnostic use in that they involve the production of a maximal or near maximal degree of adrenal cortical activation. They are, therefore, hardly suitable for precise quantitative calibration of varying levels of adrenal reserve.

Actually, it is highly probable that many patients with chronic adrenal insufficiency who do not yield a significant response to ACTH and who require maintenance substitution therapy have minute remnants of cortical tissue;[34] and it is obvious that the adrenal reserve of control subjects must vary over a considerable range. In these studies no attempt was made to characterize these fine gradations of adrenal cortical function; on the contrary, responses have been interpreted on an "all or none" basis. However, it must be recognized that in certain unusual circumstances the ACTH test—actually a measure of the capacity of the adrenal cortex to *increase* secretory function—may not accurately reflect the existing level of adrenal cortical activity. For example, it has been found that an adrenal cortical carcinoma, presumably autonomous and therefore independent of control by ACTH, may fail completely to respond to ACTH even though enormous quantities of corticosteroids are continuously secreted.[35,36] On the other hand, in agreement with Hills et al.,[37] patients have been observed who require no replacement corticosteroid therapy (under ordinary living conditions) following subtotal bilateral adrenalectomy and yet show a definitely subnormal response to ACTH stimulation. Apparently, in these patients a small cortical remnant is already responding maximally to a high circulating level of endogenous ACTH. Obviously, during periods of stress replacement therapy usually becomes mandatory. In the vast majority of patients, however, the response to intensive ACTH stimulation permits a reliable appraisal of adrenal cortical secretory function and reserve.

Finally, it is emphasized that epinephrine should not be employed as a diagnostic agent in evaluating pituitary-adrenal function since there is strong evidence that, despite the frequent occurrence of eosinopenia, epinephrine does not stimulate the pituitary-adrenal system of man.[31,38]

SUMMARY AND CONCLUSIONS

1. The response to adrenocorticotrophic hormone (ACTH) remains a highly specific test of adrenal cortical reserve.

2. The requirements for an adequate test of adrenal cortical function include: (1) A potent preparation of ACTH, access of which to the adrenal cortex is assured (minimal inactivation); (2) specific, sensitive and practical criteria of adrenal cortical stimulation.

3. A pronounced eosinopenia *following intensive adrenocortical activation with ACTH* is a reliable diagnostic index of intact adrenal cortical function. For proper interpretation, however, the intrinsic error of the eosinophil counting methods must be understood and the indirect nature of eosinopenia as an index must be recognized.

4. An increase in urinary excretion of 17-hydroxycorticoids after ACTH administration is a direct reflection of adrenal cortical activation. Attention is called to this procedure (and related methods) as a highly useful technic for the clinical laboratory.

5. The rapid ACTH test (four-hour eosinopenic response to a single intramuscular injection of ACTH) may be useful as a preliminary screening procedure. It should not be relied upon as the sole diagnostic index of adrenal cortical function.

6. Epinephrine should not be used in the evaluation of pituitary-adrenal function.

7. An eight-hour intravenous infusion of ACTH produces an intense stimulation of the adrenal cortex as reflected by a marked eosinopenia (75 per cent, or greater) and a significant rise in urinary 17-hydroxycorticoid excretion (5 mg. per twenty-four hours, or greater). These changes afford a sensitive and valid test of adrenal cortical reserve.

8. The intramuscular or subcutaneous administration of purified ACTH* in a long-acting gelatin vehicle appears to offer an alternative method of obtaining a definitive evaluation of adrenal cortical function.

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Clinical Value of the TSH Test in the Diagnosis of Thyroid Diseases*

GEORGE A. BISHOPRIC, M.D., NORMAN H. GARRETT, M.D. *and* WILLIAM M. NICHOLSON, M.D.
Durham, North Carolina

IT is possible to measure the functional capacity of the thyroid gland as well as its functioning state. The basal metabolic rate, the serum protein-bound iodine and the radioactive iodine (RAI) uptake test have proved to be extremely helpful in determining the functional status of the thyroid gland at the time of testing. However, these tests, when carried out in the usual fashion, do not reveal the functional capacity of the gland. There are common clinical diagnostic problems in which the thyroid functional state may be depressed but the capacity to function may be normal. It is in these situations that a comparison of the activity of the thyroid gland before and after stimulation by thyrotropic hormone (TSH) has proved to be of great diagnostic value.

In distinguishing between primary hypothyroidism and hypothyroidism secondary to pituitary dysfunction the response of the RAI uptake to TSH has been shown to be an accurate point of differentiation. The usual measurements of thyroid function give low results in both but the response to TSH stimulation is strikingly different. If hypothyroidism is primary, whether spontaneous or as a result of surgery or isotope therapy, there should be no response to TSH. The abnormal or largely absent thyroid gland is already functioning at its lower peak capacity, and is presumably already under maximal TSH stimulation from the pituitary in the "feed-back" mechanism. If hypothyroidism is secondary to pituitary deficiency, the thyroid gland is structurally and potentially functionally normal and a good response to TSH is expected.

It is important to establish the thyroid status of patients who are already taking thyroid medication for more or less obscure reasons. There is no real clinical difference between the adequately treated myxedematous patient and the normal patient who has been given thyroid hormone. Laboratory studies in both will show normal basal metabolic rates and normal or even elevated serum protein-bound iodine. The RAI uptake in both will be low. Evaluation of symptoms is most difficult and frequently impossible, particularly in those patients who have been taking large quantities of thyroid substance for many years. Discontinuing thyroid medication in such patients "to see what happens" is not a satisfactory solution, as the patient has often become quite emotionally attached to this drug and wants more than a conjecture as a basis for discontinuing it. Then, too, if true hypothyroidism is present, it may take several months for the symptoms and signs of myxedema to recur. Furthermore, the normal patient who has been taking thyroid may, after stopping medication, have the appearance of transient withdrawal signs and symptoms (Farquharson phenomenon) which, if sufficient time for disappearance is not allowed, may lead to an erroneous diagnosis of true hypothyroidism. An additional laboratory test that can be performed in a short period of time and with a high degree of accuracy is needed. Theoretically, the dormant gland of a normal subject on thyroid medication should respond to TSH. The RAI uptake in these patients is thought to be reduced because of the suppression of endogenous pituitary TSH by the exogenous thyroid medication. If the thyroid glands of these subjects show a consistent increase in RAI uptake after TSH stimulation, a solution to this particular diagnostic dilemma is possible.

This study is an attempt to establish the reliability of the RAI uptake response to TSH

* From the Department of Medicine, Duke University School of Medicine and Duke Hospital, Durham, N. C.
The I-131 used in these studies was obtained from the Abbott Laboratories, Inc. upon authorization and allocation by the U. S. Atomic Energy Commission.

as a diagnostic procedure, to compare the three- and twenty-four-hour RAI uptake responses to a single injection of TSH and to evaluate the regularity of the RAI uptake response to TSH in normal subjects who have been receiving thyroid for reasons other than proven hypothyroidism.

PROCEDURE

A study of thirty-four subjects is the basis for this report. These include twelve patients with hypothyroidism of thyroid origin (seven of whom were receiving thyroid medication at the time of study), six patients with hypothyroidism secondary to hypopituitarism, four normal subjects not receiving medication, ten normal subjects taking different amounts of thyroid hormone for periods of time varying from one month to ten years and two patients who inadvertently received iodine-containing substances for contrast roentgenograms just prior to study. Of the normal subjects taking thyroid substance, six were normal medical students whose RAI uptakes had been measured prior to instituting desiccated thyroid at a dose of 180 mg. daily for a period of one month.

In this study diagnostic problems were avoided. Only classic cases of myxedema proven by all available laboratory studies were accepted. The diagnosis of hypopituitarism and differentiation of primary from secondary hypothyroidism was clearly established by accepting as "secondary" only those patients with clinical and laboratory evidence of multiple glandular dysfunction of pituitary origin. Estimations of the 17-ketosteroids, gonadotropins, corticosteroids, basal metabolic rate and insulin glucose tolerance curves were obtained when indicated.

Tracer doses of from 10 to 20 microcuries of radioactive iodine (I-131) were administered. All measurements were made with an aloe scintillation counter, model NRD-SC2. The counter was adjusted to give counts of 2,000 or more with the tracer dose used at 15 cm. Day to day stability of the counting rate was maintained by checks with a radioactive cobalt standard. The thyrotropin* used was the lyophilized thyrotropic principle of bovine anterior pituitary gland. The thyroid hormone substance administered by us was in the form of desiccated thyroid.*

* The thyrotropin and desiccated thyroid used were obtained from Armour.

The technic used was similar to that of Jeffries et al.[1] except that the uptake estimations were made after three and again after twenty-four hours. On the first day the subjects were given a tracer dose of I-131 and the uptake was measured after three hours. After the twenty-four hour estimation on the morning of the second day a single injection of four U.S.P. units of TSH (10 mg. Armour $2R_3$ standard) was given intramuscularly. TSH has been shown to reach its maximal effect in twenty-four to forty-eight hours.[2] On the third day the residual amount of radioactivity in the thyroid gland was usually very small. The second tracer dose of I-131 was then given and estimations were repeated in three and again in twenty-four hours. Correction was made for the residual radioactivity from the previous tracer dose after allowing for decay. No correction was made for biologic release of the previous tracer RAI because of its variability. It was thought that the residual activity was insignificant and that the error introduced by not accounting for biologic release would be negligible in three hours, and not appreciably greater in twenty-four hours. Failing to account for this release would decrease rather than increase the apparent response. Scheduled as indicated, the entire period of testing required only four days.

The percentage differences between the two three-hour uptakes and the two twenty-four-hour uptakes is considered to be a measure of the functional capacity of the thyroid gland.

RESULTS

Normal Subjects. Four normal subjects not receiving specific medication were studied to test the technic. After TSH there was a mean increase of 19.8 in the three-hour percentage uptakes (range 17 to 21), and a mean increase of 34.5 (range 22 to 50) in the twenty-four hour RAI uptake. (Table IA.)

Normal Subjects Receiving Thyroid Medication. All ten subjects showed a notable increase in RAI uptake in three and twenty-four hours after TSH. In three hours the mean response was a rise in the percentage uptake of 10.1 (range 5 to 21). In twenty-four hours the mean response was 25.5 (range 10 to 50 per cent). All subjects had well over a 15 per cent total RAI uptake in twenty-four hours after TSH. It was observed that all of the six medical students who had previous measurements showed a rise, after TSH, to the same or greater total uptake level as

TABLE 1

Subject, Age, Race and Sex	Diagnosis	Daily Thyroid Medication	3-Hour Uptakes		Response	24-Hour Uptakes		Response
			ā/TSH (%)	p̄/TSH (%)		ā/TSH (%)	p̄/TSH (%)	
A. Normal:								
B. K., 24, W, M	Normal	None	11	32	21	24	54	30
A. E., 30, W, F	Lupus erythematosus	None	13	34	21	21	57	36
R. B., 25, W, M	Normal	None	14	31	17	23	45	22
A. C., 57, W, M	Neurosis	None	0	20	20	14	64	50
					Mean 19.8			Mean 34.5
B. Normal, Receiving Thyroid:								
N. K., 53, W, F	Non-toxic adenoma of thyroid	3 gr. for 2 mo.	8	19	11	12	36	24
L. B., 26, W, F	Normal, "sluggish"	¼ gr. for 2 mo.	1	7	6	8	30	22
H. F., 23, W, F	Normal, "sluggish"	2 gr. for 8 yr.	5	13	8	2	17	15
M. S., 30, W, F	Normal, "menstrual irregularities"	2 gr. for 10 yr.	2	9	7	8	18	10
B. M., 23, W, M	Normal	3 gr. for 1 mo.	0 (3 ā/Rx)	21	21	11 (17 ā/Rx)	48	37
D. G., 21, W, M	Normal	3 gr. for 1 mo.	0 (11 ā/Rx)	13	13	3 (22 ā/Rx)	23	20
B. O., 20, W, M	Normal	3 gr. for 1 mo.	9 (14 ā/Rx)	24	15	7 (32 ā/Rx)	45	38
R. B., 22, W, M	Normal	3 gr. for 1 mo.	4 (8 ā/Rx)	13	9	3 (18 ā/Rx)	18	15
D. E., 22, W, M	Normal	3 gr. for 1 mo.	4 (8 ā/Rx)	9	5	1 (32 ā/Rx)	25	24
T. B., 22, W, M	Normal	3 gr. for 1 mo.	19 (13 ā/Rx)	25	6	23 (24 ā/Rx)	73	50
					Mean 10.1			Mean 25.5
C. Normal, Received Iodine:								
W. A., 41, W, M	Manic-depressive reaction	None*	10	6	−4	7	3	−4
E. K., 40, W, M	Obesity	None†	.....	3	.....	5	0	−4
D. Primary Hypothyroidism, no Rx:								
M. A., 42, W, F	Primary myxedema	None	8	3	−5	3	4	1
H. P., 50, W, M	Primary myxedema	None	5	3	−2	8	15	7
A. F., 46, W, F	Postoperative myxedema	None	9	6	−3	3	4	1
J. L., 32, W, F	Post-isotope myxedema	None	5	3	−2	3	2	−1
F. B., 16, W, F	Cretinism	None	10	10	0	3	3	0
					Mean −2.4			Mean 1.6
E. Primary Hypothyroidism on Rx:								
W. P., 64, W, M	Primary myxedema	1½ gr. for 3 yr.	2	6	4	1	8	7
C. H., 35, W, F	Primary myxedema	1½ gr. for 9 yr.	0	6	6	2	3	1
V. H., 36, W, F	Primary myxedema	1½ gr. for 2 yr.	.....	5	.....	2	0	−2
L. T., 48, W, F	Primary myxedema	1½ gr. for 2 yr.	3	7	4	2	0	−2
N. W., 38, W, M	Primary myxedema	1 gr. for 2 yr.	1	4	3	3	0	−3
C. W., 50, W, F	Postoperative myxedema	3 gr. for 15 yr.	3	3	0	0	10	10
H. F., 42, W, F	Postoperative myxedema	1½ gr. for 1 mo.	.....	5	.....	2	0	−2
					Mean 3.4			Mean 1.3
F. Secondary hypothyroidism:								
J. P., 53, W, M	Hypopituitarism (pituitary tumor)	None	11	21	10	10	21	11
R. W., 41, C, M	Hypopituitarism (pituitary tumor and x-ray Rx)	None	7	21	14	18	53	35
M. F., 45, W, F	Sheehan's syndrome	None	2	13	11	15	52	37
B. G., 19, W, F	Hypopituitarism	None	13	10	−3	5	28	23
W. C., 27, C, M	Hypopituitarism, post-operative pituitary tumor	None	14	20	6	10	24	14
M. R., 51, W, F	Hypopituitarism	1 gr. for 1 yr.	8	14	6	15	13	−2
					Mean 7.3			Mean 19.7

* Recent i.v. pyelograms.
† Recent gallbladder series.

existed prior to depression of uptake by thyroid hormone. (Table IB.)

Normal Subjects Who Received Iodine. The two patients who were given iodine compounds for x-ray studies had no response to TSH. That there is actually a fall in the uptake relates to the recent administration of the iodine-containing substances and further accumulation of iodine in the gland between the two uptakes. (Table IC.)

Subjects with Primary Hypothyroidism. In five patients with primary hypothyroidism not under treatment (Table ID), the response in three hours was a change of −2.4 in the percentage uptake (range −5 to 0). In twenty-four hours the mean response was 1.6 (range −1 to 7). In no case was the total twenty-four-hour uptakes greater than 15 per cent after TSH although one patient did reach that level. This patient had classical findings of myxedema of very recent onset.

In seven patients with primary hypothyroidism receiving treatment (Table IE) the average response in the uptake in three hours was 3.4 (range 0 to 6). The average twenty-four-hour response was an increase in the percentage uptake of 1.3 (range −3 to 10). Again, in no case was the total twenty-four hour percentage uptake normal after TSH. The one case that showed an uptake increase of 10 was a patient with post-thyroidectomy myxedema.

Subjects with Secondary Hypothyroidism. Of six patients with hypothyroidism secondary to pituitary failure (Table IF) five showed an increase in the RAI uptake after TSH stimulation. The mean response, including all six cases, was an increase of 7.3 in the percentage uptake in three hours (range −3 to 14) and 19.7 in twenty-four hours (range −2 to 37). All, save for the one unresponsive patient, showed total RAI uptakes greater than 15 per cent in twenty-four hours after TSH stimulation.

COMMENTS

The response of the RAI uptake to TSH stimulation has become a practical laboratory diagnostic procedure since a highly purified thyrotropic substance was made generally available. Before the availability of RAI uptake studies, Scowen in 1937 showed that after TSH stimulation the basal metabolic rate increased markedly in normal subjects and in patients with hypothyroidism secondary to pituitary dysfunction, but did not rise in patients with myxedema of primary (thyroid) origin.[3] Using the RAI uptake as a measuring device, other recent studies have confirmed and amplified these earlier conclusions, and have made further note of the value of the RAI uptake response to TSH in diagnosing obscure hypothyroidism.[4–6] The results of our studies clearly support and emphasize the value of this test as a diagnostic aid.

The results of this study clearly differentiate between euthyroid patients whose RAI uptake has been suppressed by administration of thyroid substance and patients with primary hypothyroidism. An increase in the twenty-four hour uptake percentage of 10, after TSH stimulation, appears to be the upper limit of response compatible with a diagnosis of primary hypothyroidism. Of the patients with primary hypothyroidism studied, none had a total twenty-four-hour uptake greater than 15 per cent after TSH stimulation. On the other hand, no normal subject, with or without medication, had an increase of less than 10 in the twenty-four-hour percentage uptake after TSH stimulation. No normal subject had less than 15 per cent total twenty-four-hour RAI uptake after TSH. In five of six patients with hypothyroidism secondary to pituitary dysfunction there was clear differentiation from primary hypothyroidism by this test. Of the five patients who showed response, none had an increase of less than 11 in the percentage uptake in twenty-four hours, and all were well within the normal twenty-four-hour uptake range. The reason for the lack of response in one patient (M. R.) is uncertain. Perhaps this patient would have shown an increase in uptake after multiple TSH injections, as shown by other workers. Querido and Stanbury,[4] however, reported a case of hypopituitarism in which they were unable to produce an increase in uptake after nine days of TSH stimulation. They note Sheehan's postulation that a gland, unstimulated by TSH, might in time become fibrotic and unresponsive.

Using the response of the three-hour uptake of RAI after TSH in a manner similar to that of Jeffries et al.,[1] we were able to confirm their results, within limitations. There was a significant difference in the response of subjects with primary hypothyroidism as compared with normal subjects whether or not receiving thyroid medication. Using the three-hour uptake, and establishing a TSH response as 6 per cent or less and a total three-hour RAI uptake of 8 per cent or less as criteria for the diagnosis of hypothyroidism of primary etiology, this group can be

distinguished from the normal and secondary hypothyroidism groups with little overlap. It will be noted from a survey of the tables that the differences in three-hour uptakes and responses are so small that, at least with our available equipment and technic, small experimental errors might readily invalidate the results. It is apparent that it is only by chance this did not happen in our series. For this reason we believe that the comparison of twenty-four-hour responses and uptakes, with more widely separated values and clearer differences, is more reliable.

SUMMARY

The change in the twenty-four-hour RAI uptake of the thyroid gland after stimulation with a single injection of TSH is a reliable and valuable diagnostic aid in distinguishing between primary and secondary hypothyroidism. It is also of particular value in differentiation between primary hypothyroidism and euthyroidism in patients whose thyroid function has been suppressed by substitution therapy and whose clinical and laboratory picture otherwise is similar. The technic used, that is, a single injection of TSH and a total of only four days' observation, seems to be at least as reliable as technics involving multiple injections of TSH and much longer periods of observation. The three-hour uptake response to TSH parallels the twenty-four hour response but does not seem to be as safe a diagnostic aid because of relatively larger experimental error. An upper limit of increase of 10 in the twenty-four-hour percentage uptake after TSH, and an upper limit of 15 per cent in the total twenty-four-hour RAI uptake after TSH, seem to be the highest values acceptable for the diagnosis of primary dysfunction of the thyroid gland.

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Studies of 17-Hydroxycorticosteroids*

VI. Circulating Concentrations in Patients with Rheumatic Fever

VINCENT C. KELLEY, M.D., ROBERT S. ELY, M.D., ALAN K. DONE, M.D. *and* LORIN E. AINGER, M.D.

Salt Lake City, Utah

A VARIETY of chemical abnormalities which occur in the blood of patients with acute rheumatic fever have been described during the past few years. Among these is the first appearance, or appearance in increased titer, of specific anti-streptococcal antibodies reflecting the preceding streptococcal infection.[1] Characteristic changes in the distribution of the electrophoretic protein fractions likewise occur.[2–7] In addition, many non-specific changes occur in the blood, the substances with serum levels non-specifically but characteristically altered during the acute phase of disease being termed "acute phase reactants."[8] Among the acute phase reactants and reactions may be mentioned the erythrocyte sedimentation rate, the non-specific hyaluronidase inhibitor,[9–12] serum mucoproteins,[13–16] C-reactive protein,[17–21] serum complement,[22] bactericidins,[23–25] serum hexosamines,[26–29] serum non-glucosamine polysaccharides,[8,28,30–32] the diphenylamine reaction[33,34] and the quaternary ammonium salt reaction.[35,36] This list could be extended considerably if all substances and reactions which have been suggested[37] as belonging to this group were included.

Evidence has been presented previously[10,11,16,38–40] that serum concentrations of certain acute phase reactants are controlled or greatly influenced by the adrenal cortex and that cortisone exerted the most profound effects among the adrenal hormones studied. Since the levels of these acute phase reactants are increased in the blood of patients with acute rheumatic fever and approach normal again as the disease becomes quiescent it seems possible that an altered adrenal cortical function exists in patients with this disease.

The introduction by Nelson and Samuels[41] of a technic for the determination of 17-hydroxycorticosteroid concentrations in blood permits a more direct investigation of this possibility than have previously available methods. The 17-hydroxycorticosteroids measured by this technic include compound F (17-hydroxycorticosterone, hydrocortisone), compound E (17-hydroxy-11-dehydrocorticosterone, cortisone) and compound S (17-hydroxy-11-desoxycorticosterone). It has been demonstrated[42] that in man the principal adrenal cortical hormone is compound F and that at most only minimal amounts of compounds E and S are formed. Therefore, measurements of 17-hydroxycorticosteroid concentrations in human blood essentially reflect the circulating concentrations of compound F, the principal adrenal cortical hormone.

In the present study plasma 17-hydroxycorticosteroid concentrations were determined in patients with various phases of rheumatic fever in an attempt to evaluate the role of the adrenal cortex in this disease.

MATERIALS AND METHODS

The subjects included in this study were 212 children ranging in age from two and one-half to sixteen years. The "well-control" subjects consisted of a group of forty children.[43] The remaining 172 subjects were twenty-seven children with chorea and 145 with other manifestations of rheumatic fever (fifty-eight with active and eighty-seven with inactive rheumatic fever). The diagnosis of rheumatic fever in these patients was made in conformity with the criteria of Jones.[44] Patients were included in the category of "inactive rheumatic fever" only if they met each of the following criteria: (1) Normal

* From the Lockhart Memorial Laboratory, Department of Pediatrics, University of Utah College of Medicine, and the Heart Laboratories of the Utah State Rheumatic Fever Clinics, Salt Lake City, Utah. This work was supported by research grants from the American Heart Association and the Helen Hay Whitney Foundation.

erythrocyte sedimentation rate and no clinical signs of rheumatic activity at the time of sampling, (2) symptom-free for a minimum of six months since their last attack of acute rheumatic fever, (3*a*) had been observed by one of the authors during an acute attack of rheumatic fever or (3*b*) had been observed by one of the authors' predecessors in the University of Utah Department of Pediatrics or the Utah State Rheumatic Fever Clinics during a preceding unequivocal attack of rheumatic fever and at the time of sampling had characteristic residual cardiac murmurs.

Blood samples were obtained by venipuncture, the plasma being separated by centrifugation and stored in deep-freeze until used. Determinations of plasma 17-hydroxycorticosteroid concentrations were made by the method of Nelson and Samuels.[41]

OBSERVATIONS

As shown in Figure 1 the 17-hydroxycorticosteroid concentration in the blood of patients with active rheumatic fever was related to the duration of the illness. Elevated plasma concentrations of 17-hydroxycorticosteroids were observed in all patients studied during the first few days of rheumatic activity. These concentrations at first rapidly and then more slowly decreased in such a manner that the curve describing the relationship between the mean concentrations of 17-hydroxycorticosteroids and the duration of illness approximates an hyperbola. This is shown in Figure 1 by the heavy line.

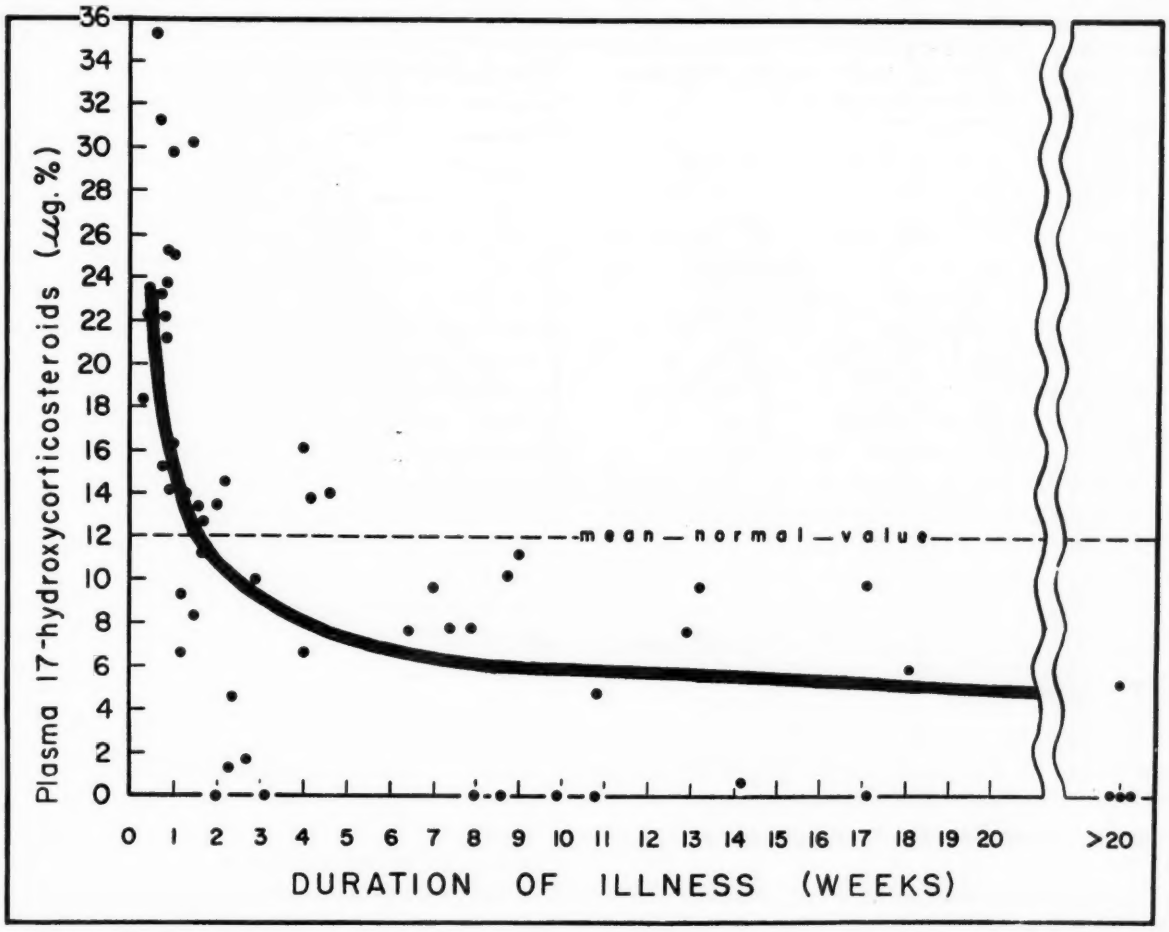

FIG. 1. Plasma 17-hydroxycorticosteroid concentrations in patients with untreated active rheumatic fever.

Table 1 presents data concerning 17-hydroxycorticosteroid concentrations in patients with various phases of rheumatic fever. Those patients designated as having "early acute" rheumatic fever had been ill for not more than one week. In this group, as shown in Table 1, the mean plasma 17-hydroxycorticosteroid concentration was 23.1 $\pm$ 1.49 μg. per cent. This value is significantly elevated as compared to the mean value observed in the control group of children ($p < .01$).

During the second week of active rheumatic

fever the 17-hydroxycorticosteroid values were extremely variable. In Table 1 the patients in this group are designated as having a "transitional phase" of rheumatic activity. In this group the mean steroid concentration was 11.8 ± 2.01 μg. per cent, a value which does not

TABLE 1
CIRCULATING CONCENTRATIONS OF 17-HYDROXYCORTICOSTEROIDS IN PATIENTS WITH VARIOUS PHASES OF RHEUMATIC FEVER (R.F.)

Group	No.	17-Hydroxycorticosteroids (μg. %)			
		Mean	S.E.M.	Range	P (vs. controls)
Controls	40	12.0	±1.29	0–28.7	.....
"Early acute" R.F.	15	23.1	±1.49	14.1–35.2	<.01
"Transitional phase" R.F.	12	11.8	±2.01	0–30.2	>0.5
"Well established active" R.F.	31	5.9	±0.93	0–16.1	<.01
Inactive R.F.	87	8.3	±0.61	0–19.8	<.01
Chorea	27	5.7	±0.86	0–12.8	<.01

differ statistically from that of the control group. The wide variations observed in this group (0–30.2 μg. per cent) probably are attributable to: (1) the rapid decrease in circulating concentrations of 17-hydroxycorticosteroids which occurs after the first few days of illness, (2) inaccuracies in determining precisely the date of initial symptomatology in many patients, (3) variations in the severity of the disease, and (4) probable individual variations in the endocrine response to the stress occasioned by the illness.

Those patients designated as having "well established active" rheumatic fever had been ill with their disease for more than two weeks. In this group of patients the mean concentration of 17-hydroxycorticosteroids (Table 1) was 5.9 ± 0.93 μg. per cent, a figure significantly lower than the mean value observed in the control groups ($p < .01$).

Patients with inactive rheumatic fever in this series had a mean plasma 17-hydroxycorticosteroid concentration of 8.3 ± 0.61 μg. per cent. This value also is significantly lower than that observed in the control group ($p < .01$). Likewise, patients with Sydenham's chorea had 17-hydroxycorticosteroid concentrations significantly lower than those seen in the control group of children (mean 5.7 ± 0.86 μg. per cent; $p < 0.01$).

Figure 2 represents graphically the distribution of steroid concentrations observed in patients belonging to the following categories: early acute rheumatic fever (Fig. 2A), well established active rheumatic fever (Fig. 2B), inactive rheumatic fever (Fig. 2C) and chorea (Fig. 2D). In these graphs the distribution of values within each group is compared individually with that within the control group. In each graph the distribution for the control group is indicated by the heavy line, superimposed over the distribution for the particular rheumatic group (indicated by the shaded area). From the four graphs of Figure 2 it may be seen that, as judged by distribution of 17-hydroxycorticosteroid concentration, each of the study groups represents a population different from the normal. Figure 2A shows that the 17-hydroxycorticosteroid concentrations in all of the patients with early acute rheumatic fever are higher than the mean normal value and that only 42 per cent of the values observed in the control group are as high as the lowest value in the group with early acute rheumatic fever. However, in patients with well established active rheumatic fever, with inactive rheumatic fever and with chorea, the converse situation generally obtains. As shown in Figure 2B, C and D, the distribution of 17-hydroxycorticosteroid values in these groups of patients is definitely lower than in the control group.

DISCUSSION

In patients with rheumatic fever the 17-hydroxycorticosteroid plasma level is related to the duration of illness in such a manner that the curve depicting the relationship between the two approximates an hyperbola, with the initially elevated steroid concentrations decreasing to subnormal levels relatively soon following the onset of illness. The observation of these elevated steroid concentrations in early acute rheumatic fever is in conformity with that of similar elevations in a variety of other acute illnesses.[42,45,46] Such elevations are apparently non-specific. Various acute phase reactants likewise exhibit similar elevations in acute rheumatic fever.[8–12,15,16,21,26–28] The concentrations of these substances also are maximal very early in the course of the disease and gradually decrease thereafter. Furthermore, the occurrence of increased concentrations of acute phase reactants is a nonspecific phenomenon, all of these substances showing elevations in a variety of acute diseases and "stress" situations. Thus except for varia-

tions in temporal sequence the responses of circulating 17-hydroxycorticosteroids and of certain acute phase reactants are similar during the course of active rheumatic fever.

That this similarity may be more than coincidental is implied by the results of certain animal alterations of adrenal cortical function in these individuals.

Further evidence implying such a relationship may be deduced from the data concerning patients with chorea and with inactive rheumatic fever. It has been demonstrated[9] that the non-

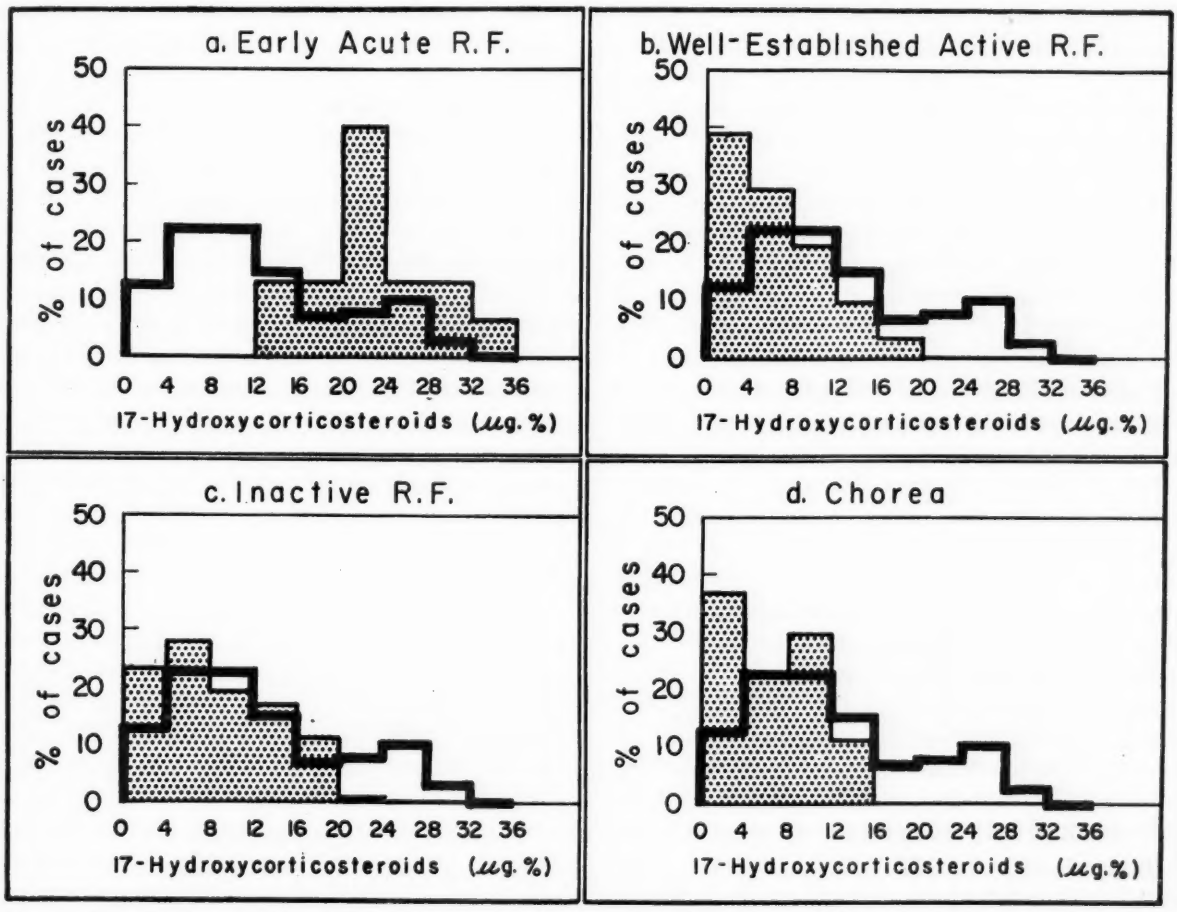

FIG. 2. Distribution of 17-hydroxycorticosteroid concentrations in patients with various phases of rheumatic fever. (Distribution in the control group is indicated by the superimposed heavy line and distribution in the study groups by the shaded areas.)

experiments. The elevations of acute phase reactants observed in intact animals subjected to non-specific stress are not observed in similarly stressed adrenalectomized animals.[38–40] On the other hand, adrenalectomy does not abolish the elevations produced by cortisone administration.[39] These results suggest a function of adrenal cortical steroids in affecting the levels of certain acute phase reactants. Such observations, together with the similar responses of acute phase reactant and 17-hydroxycorticosteroid levels in active rheumatic fever, indicate that elevations of certain acute phase reactants in rheumatic fever patients may be related to specific hyaluronidase inhibitor level is abnormally low in patients in these categories. The data presented here indicate that the same is true of circulating 17-hydroxycorticosteroid concentrations. Evidence suggesting that the abnormally low concentrations of the hyaluronidase inhibitor observed in patients with inactive rheumatic fever probably existed before the onset of the disease rather than as a result of it has been presented by Adams, Glick, Anderson and Dwan.[47] These investigators reported that siblings and parents of patients with rheumatic fever had lower inhibitor levels than did a normal control group. The possibility that

a similar situation may exist with regard to circulating 17-hydroxycorticosteroid concentrations is being investigated in this laboratory at the present time.

In patients with rheumatic fever, after the early acute phase, the steroid concentrations decreased uniformly to low values. Whereas not much importance can be attributed to a single low plasma 17-hydroxycorticosteroid value, consistently low values in the same individual or in a group of individuals in the same clinical classification are significant. This does not mean necessarily that the adrenal cortex does not or cannot produce its hormones as rapidly or in so great a quantity as in the normal individual. An attractive alternative explanation is that such individuals destroy or remove adrenal steroids from the blood more rapidly than they are replaced by the adrenal cortex. Also it seems possible that some adrenal hormone other than 17-hydroxycorticosterone may be present in the blood of these individuals in sufficient concentration to pre-empt the role of the latter in regulating pituitary release of ACTH. Thus the equilibrium state with regard to release of pituitary ACTH might be such as to provide insufficient stimulation to the adrenal cortex to maintain the circulating concentration of 17-hydroxycorticosteroids as high as they are in the "normal" individual. Even though one of these latter explanations were indeed correct, the steady state with regard to 17-hydroxycorticosteroids in these individuals indicates that the adrenal cortex is not producing these steroids rapidly enough to maintain a "normal" concentration in the blood. Therefore, homeostatic mechanisms which are adequate to maintain a certain level of circulating 17-hydroxycorticosteroids in the "normal" individual are not adequate to maintain a similar level in these patients.

It has been demonstrated that many patients with low circulating concentrations of 17-hydroxycorticosteroids respond to the administration of exogenous ACTH with satisfactory increases in their steroid levels.[48] This combination of low steroid concentrations with the ability to increase these concentrations adequately in response to sufficient ACTH stimulation is considered as indicating "relative adrenal insufficiency." Adrenalectomized animals and patients with Addison's disease also have abnormally low circulating concentrations of 17-hydroxycorticosteroids but they are incapable of producing steroid elevations in response to ACTH stimulation—either endogenous or exogenous. The term "relative adrenal insufficiency" employed in this discussion is not to be confused with the absolute adrenal insufficiency which exists in these latter subjects.

Patients in the categories of "well established active" rheumatic fever, inactive rheumatic fever and chorea exhibit "relative adrenal insufficiency." The occurrence of elevated 17-hydroxycorticosteroid concentrations during the "early acute" phase of rheumatic fever suggests that a heightened stimulus for adrenal cortical secretory activity exists at this time. It also suggests that the adrenal cortex of the rheumatic fever patient is capable of responding to this stimulus, at least early in the course of the illness. Elevated plasma steroid concentrations occur not only in patients suffering initial attacks of rheumatic fever but also in those suffering acute recurrences of the disease. Since the latter group consists of individuals who had inactive rheumatic fever before the onset of their acute recurrences, it seems that the adrenal cortex of the patient with inactive rheumatic fever also is capable of responding to potent endogenous stimulation. Thus the finding of elevated plasma steroid levels in patients with early acute rheumatic fever is interpreted as indicating a "stress response." The subsequent depression of these steroid levels to abnormally low values during continuing rheumatic activity indicates a relative failure of the adrenal cortex to comply with demand. This, combined with the demonstrated ability of these patients to produce adequate elevations of steroid levels in response to exogenous ACTH,[48] suggests that a "relative adrenal insufficiency" exists in patients with rheumatic fever.

Existing data do not eliminate the possibility that the anterior pituitary rather than the adrenal cortex is to be implicated in the failure of patients with certain phases of rheumatic fever to maintain usual circulating concentrations of 17-hydroxycorticosteroids. Recently reported preliminary data concerning circulating concentrations of endogenous ACTH in human subjects[49] make this possibility appear remote inasmuch as patients with "well established" active rheumatic fever frequently have elevated circulating concentrations of endogenous ACTH. A more comprehensive investigation of this aspect of the problem is in progress.

It is not clear from the data at hand whether

relative adrenal insufficiency is a factor in the pathogenesis of rheumatic fever or a result of the disease. Recent genetic studies indicate that inheritance of susceptibility to rheumatic fever is probably a reality.[50] If, as seems possible from analogy with published data concerning the non-specific hyaluronidase inhibitor,[47] the relative adrenal insufficiency antedates the occurrence of rheumatic fever in an individual, it seems at least possible that the hereditary trait which determines rheumatic fever susceptibility might be this relative adrenal insufficiency.

The demonstrated efficacy of prophylaxis in preventing rheumatic recurrences implies that a similar efficacy in preventing the initial attacks of rheumatic fever is possible, were there a means of consistently detecting susceptible individuals. Any measurable chemical or physiologic abnormality occurring regularly in patients with inactive rheumatic fever or chorea —two groups known to be rheumatic fever-susceptible—may well occur with similar regularity in other rheumatic fever-susceptible individuals. Thus the observations reported here of low plasma 17-hydroxycorticosteroid levels in patients with inactive rheumatic fever and with chorea deserve extensive investigation.

SUMMARY AND CONCLUSIONS

1. Plasma 17-hydroxycorticosteroid concentrations were measured in patients in various phases of rheumatic fever activity.

2. These concentrations were elevated early in the course of acute rheumatic fever and decreased as the disease progressed.

3. Patients with well established active rheumatic fever, inactive rheumatic fever and Sydenham's chorea had circulating concentrations of these steroids significantly lower than the control group.

4. Certain implications of these findings are discussed.

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Evaluation of Prolonged Cortisone Therapy in Rheumatoid Arthritis*

A Four-year Study

JOSEPH J. BUNIM, M.D.,† MORRIS ZIFF, M.D. *and* CURRIER MCEWEN, M.D.
New York, New York

THE purpose of this report is to present the data collected from observations over a four-year period, from July 1, 1949, to June 30, 1953, of seventy-eight patients with rheumatoid arthritis who were treated with cortisone or hydrocortisone for intervals varying from a few weeks to almost four years. The patients were examined about every four weeks during the study. The patients were drawn from diverse economic strata, ranging from a few in the higher income brackets to many in the indigent group. No apparent difference in the response to treatment or in the nature, frequency and severity of the side effects was noted among the different socio-economic groups.

Fourteen of the seventy-eight patients failed to report for follow-up studies or else transferred to other physicians or clinics for medical care, leaving an "abiding" group of sixty-four. Of the fourteen who dropped out seven had received cortisone under our care for at least six weeks or longer and have been included in the tables which total seventy-one patients. The seven patients who were given cortisone for less than six weeks were eliminated from the series since treatment was considered too brief to warrant conclusions as to efficacy of the steroid. In June, 1953, when data collected during the four-year period were analyzed, twenty-eight of the sixty-four patients in the series (44 per cent) were receiving cortisone or hydrocortisone daily; thirty-one were no longer getting hormone and five patients were dead. The five deaths will be analyzed in greater detail later. The prevalence in our series of certain clinical features associated with rheumatoid arthritis is listed in Table I. It will be noted that whereas the occurrence of subcutaneous nodules was of average frequency, the number of patients with juvenile rheumatoid arthritis and with psoriasis was about three times the average frequency.

TABLE I
COMPOSITION OF SERIES

Total no. given cortisone	78
Received cortisone 6 weeks or longer	71
"Abiding" group	64
No. of juvenile patients	9 (14%)
No. with psoriasis	9 (14%)
No. with spondylitis	7 (11%)
No. with subcutaneous nodules	15 (23%)

Age and Sex Distribution. Forty-eight per cent of the group were above age fifty, 35 per cent were between ages twenty and fifty and 17 per cent were below age twenty. The ratio of females to males was 4:3. (Table II.)

Duration of Arthritis. Twenty-six per cent of the series had had arthritis for less than one year at the time cortisone therapy was instituted. In 41 per cent the disease began between one and ten years prior to therapy and in 33 per cent it had lasted longer than ten years. (Table III.)

Stage of Arthritis. The criteria of the American Rheumatism Association[1] were applied in determining the stages of the disease. (Table IV.) Twenty-four per cent were in the early, readily reversible phase of arthritis exhibiting no erosion of cartilage or destruction of bone in roentgenograms (Stage I). An equal number

* From the Department of Medicine and the Study Group on Rheumatic Diseases, New York University College of Medicine, New York, N. Y. This study was supported by research grants from the Masonic Foundation for Medical Research and Human Welfare, the National Institute of Arthritis and Metabolic Diseases (P.H.S. Grant No. A-23), and the Merck Foundation for Medical Research.

† Present address: National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda 14, Md.

were in the next stage (Stage II) and about half of the group had advanced rheumatoid arthritis (Stages III and IV).

Average Daily Maintenance Dose. In calculating maintenance dose the conventional high doses given during the initial week of therapy were not included nor were the occasional transient brief increases in dosage included. The amounts listed in Table V represent daily doses on which patients were maintained for the greatest part of their courses. Our experience during the first year of this study made us conclude that it was not safe to exceed a maintenance daily dose of 100 mg. since in each of the three cases in which this level was exceeded, gastric or duodenal ulcers developed; of these, two ulcers perforated.

Duration of Cortisone Therapy. As the study progressed the series increased in size so that the total number of patients included was not reached until the last twelve months of the four-year period. Of the entire group only eleven patients were observed longer than forty-two months and nine of these were receiving cortisone at the end of this period. Of sixty-one patients who remained under our observation for twelve months after cortisone therapy had been started, forty-five took cortisone continually for longer than six months and thirty-nine for more than twelve months. (Table VI and Figure 1.) Cortisone was discontinued for one of three reasons. In some patients administration of hormone was stopped because the arthritis had improved and cortisone was no longer necessary; in some improvement was so slight that continuation of cortisone was unwarranted; and in others undesirable side effects contraindicated further treatment.

As was stated, seventy-one patients received cortisone for six weeks or longer. Six months following the beginning of cortisone administration the total had fallen from seventy-one to sixty-one patients. Care was taken to include

TABLE II
AGE AND SEX DISTRIBUTION

Age (yr.)*	Male	Female	Total
0–9	2	1	3
10–19	2	5	7
20–29	3	3	6
30–39	1	6	7
40–49	5	8	13
50–59	12	10	22
60–69	6	5	11
70 or over	0	2	2
Total	31	40	71

* Age at time cortisone therapy was begun.

TABLE III
DURATION OF ARTHRITIS (PRIOR TO MEDICATION)

Less than 6 months	9
6 to 12 months	10
13 months to 3 years	12
4 to 5 years	5
6 to 10 years	12
11 to 15 years	16
Over 15 years	7
Total	71

TABLE IV
STAGE OF ARTHRITIS*—(AT START OF THERAPY)

Stage I (early)	17
Stage II (cartilage erosion)	18
Stage III (bone destruction and deformity)	27
Stage IV (ankylosis)	9
Total	71

* Classification of American Rheumatism Association.

TABLE V
AVERAGE DAILY MAINTENANCE DOSE

Dose	No. of Patients
25–50 mg.	18
60–75 mg.	21
80–100 mg.	22
Over 100 mg.	3*
Total	64

* Each of these three patients (treated during first year of our experience) developed a gastric or duodenal ulcer; two of the ulcers perforated.

TABLE VI
DURATION OF CORTISONE THERAPY

Period from Start of Cortisone (mo.)	No. under Observation	No. Receiving Cortisone
6	61	45
12	61	39
18	55	31
24	46	21
30	32	16
36	16	12
42	11	9

these ten patients in the tabulation of therapeutic results (Table VII) at the grade given during their last visit in order to avoid bias, since some of them might have discontinued therapy or left our care because the effects were not satisfactory.

It will be noted from Table VII that 23 per cent were in remission, 28 per cent had major improvement, 43 per cent showed minor improvement and 6 per cent failed to derive any benefit from cortisone.

The relation of therapeutic response to duration of treatment is presented in Figure 2. The number and percentage of patients who had remissions increased as treatment was extended from six to twelve months. Beyond this period the proportion of patients in the four graded groups shifted moderately but at all intervals the majority showed a Grade I or II response as hormone administration continued. The correlation between duration of arthritis and response to therapy is quite definite. (Fig. 3.) The most striking response was observed in the group that had arthritis for one year or less and the least favorable effect in the group that had the disease for longer than ten years. Inconsistent and puzzling results were observed in the patients who had arthritis longer than fifteen years but this group consisted of only seven patients and the relation therefore may not be significant.

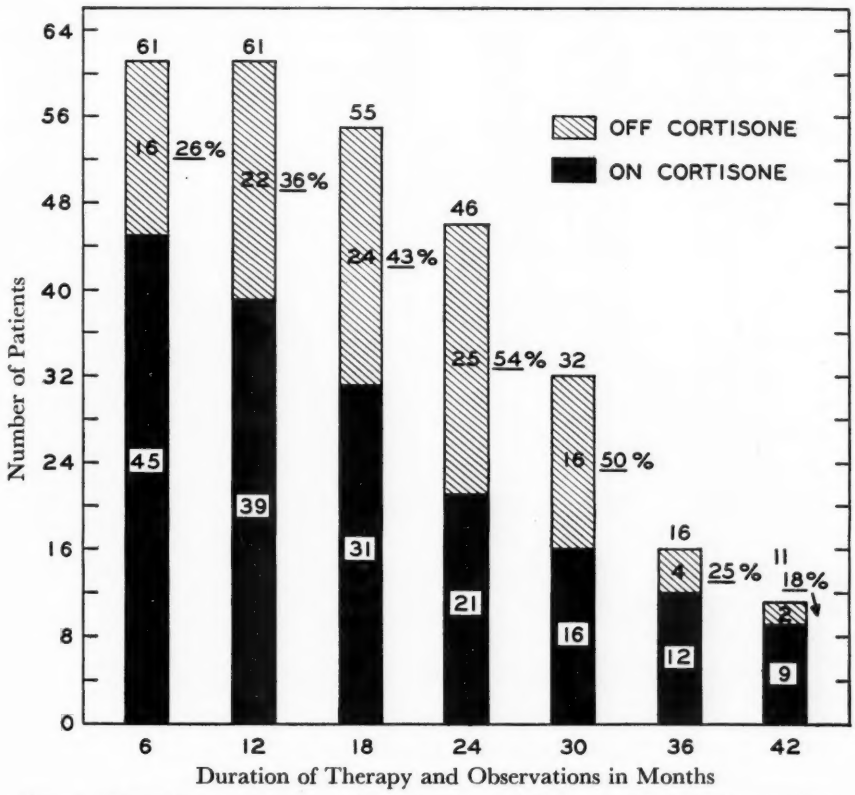


FIG. 1. Duration of cortisone administration related to period of observation.

RESULTS

In evaluating the therapeutic response, the criteria of the American Rheumatism Association[1] were used with one exception. Patients who presented no clinical evidence of activity of the rheumatoid process such as joint pain, stiffness, tenderness, swelling, warmth, redness or elevated temperature were given a Grade I rating even if the erythrocyte sedimentation rate (ESR) had not returned to normal. This exception was made in four of the sixteen patients considered to be in remission. Estimation of the results was made during the visit immediately prior to June 30, 1953.

TABLE VII

RESULTS IN SEVENTY-ONE RHEUMATOID PATIENTS TREATED WITH CORTISONE

Remission (Grade I)	16 (23%)
Major improvement (Grade II)	20 (28%)
Minor improvement (Grade III)	31 (43%)
No improvement or worse (Grade IV)	4 (6%)

Effect on Functional Capacity. In making this assessment four different criteria were used:

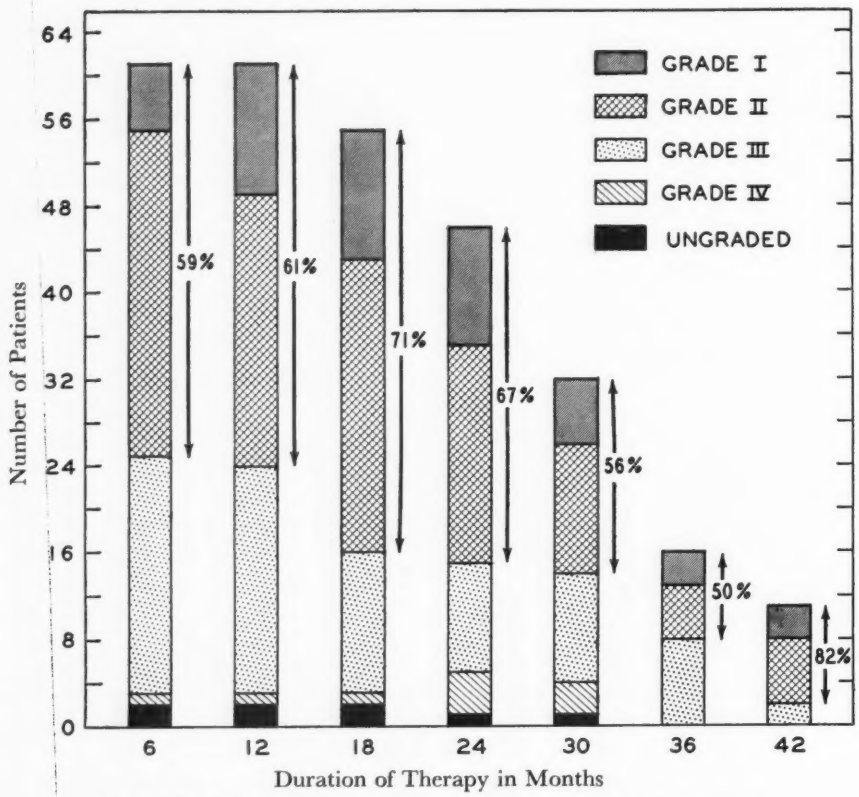


FIG. 2. Relation of therapeutic response to duration of treatment.

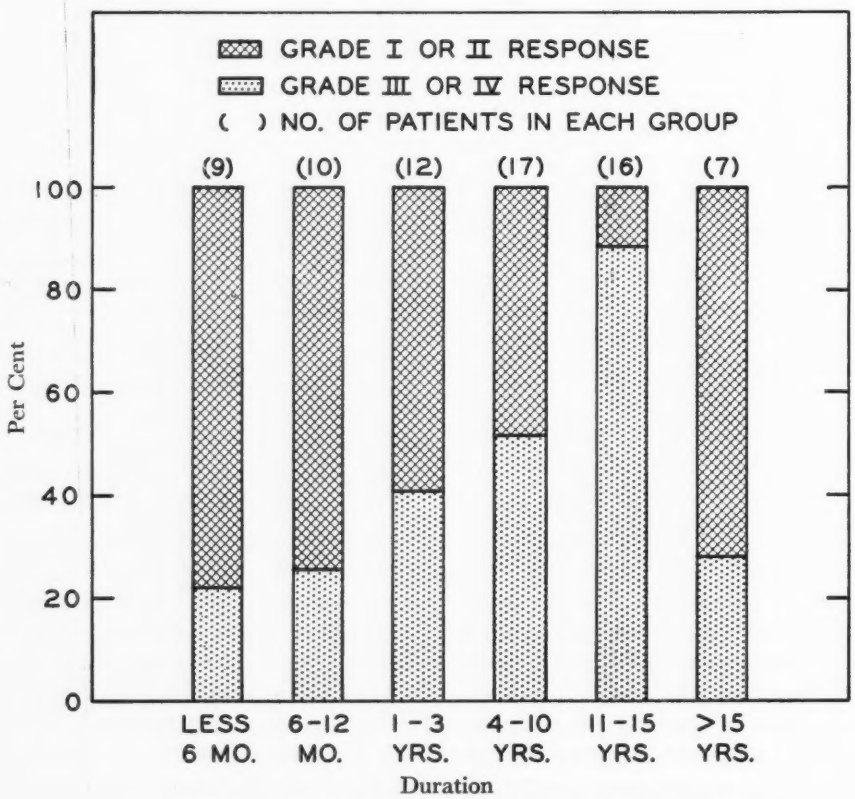


FIG. 3. Relation of therapeutic response to duration of arthritis.

(1) functional capacity according to the classification of the American Rheumatism Association (Class I, II, III and IV),* (2) employability (full-time, part-time or unemployable), (3) ability to walk (ambulatory; and semi-ambulatory, i.e., with aid of cane, crutches or wheel chair; or bedridden) and (4) self-sufficiency (for feeding, dressing and toilet needs).

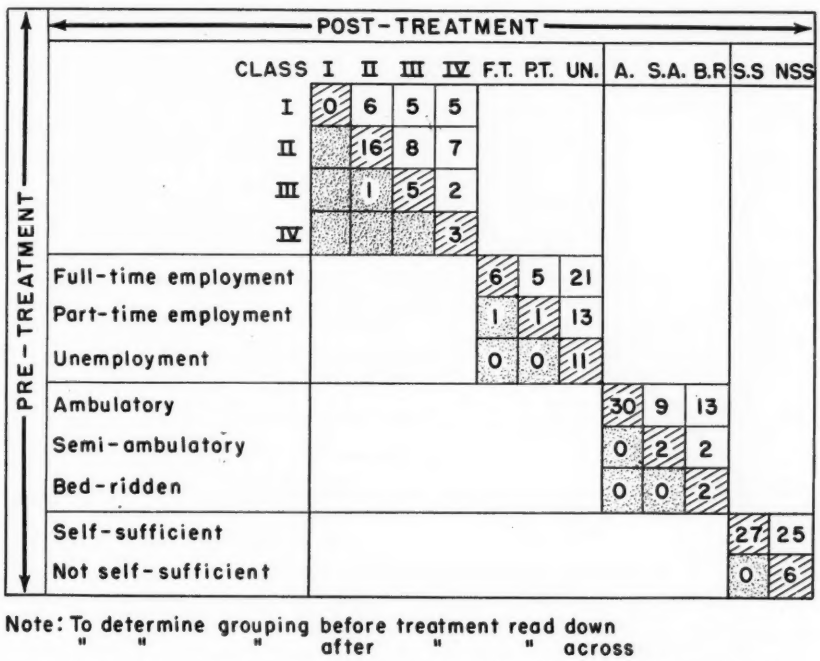


FIG. 4. Achievement record of fifty-eight patients treated with cortisone.

The changes in functional capacity of fifty-eight patients† treated with cortisone as gauged by the four criteria mentioned above are charted in Figure 4. Each of the four categories of criteria is subdivided into as many vertical and horizontal columns as there are classes within that category. The number of patients in each class before treatment will be found by totalling the numbers in all the squares of a given vertical column. In the squares which are diagonally cross-hatched will be found the number of patients who did not improve following cortisone treatment. The number in the square above the one with diagonal stripes indicates the number of patients who advanced one grade. The number in the second square above the striped one indicates an advance of two grades, etc. The number in the square below the striped one indicates regression by one grade.

Graded according to the functional classes adopted by the American Rheumatism Association, none of the patients were in Class I when cortisone was first administered. Twenty-three patients were in Class II before treatment (6 + 16 + 1). Following treatment, sixteen of this group remained in Class II, six advanced to Class I and one patient regressed to Class III. Eighteen patients were in Class III before treatment. Five remained in Class III, eight advanced to Class II and five to Class I. Seventeen patients were in Class IV before treatment. Three remained in Class IV, two advanced to Class III, seven to Class II and five to Class I.

Seven patients were employed full-time before treatment was begun; one of these regressed to a state of only part-time employment. Of the six patients who were employed part-time before treatment five became employable full-time. Forty-five of the fifty-eight patients were unemployable before treatment.* Twenty-one improved to the extent that they took full-time

* Class I: Complete function or ability to carry on all usual duties without handicaps.
Class II: Adequate function for normal activities despite discomfort.
Class III: Limited function or capable of little or none of duties of usual occupation or self-care.
Class IV: Largely or wholly incapacitated, bedridden or confined to wheel chair.

† The fifty-eight patients were unselected; all those in whom the necessary data were available were included.

* A housewife unable to do her housework was considered "unemployable."

jobs, thirteen part-time jobs and only eleven remained unemployable.

Seventeen patients were bedridden before cortisone was administered; after taking cortisone thirteen of the seventeen (76 per cent) were able to walk without any aid, two required a cane, crutch or wheel chair and only two remained bedridden.

Thirty-one patients were incapacitated and unable to take care of their daily personal needs before therapy; of these twenty-five (80 per cent) became self-sufficient after cortisone was administered.

Analysis of Cases with Remission. Eight of the sixteen patients who experienced a remission of arthritis had the disease for less than one year and five for longer than five years. (Table VIII.) Eighty per cent of the patients who exhibited remission had reversible disease (Stage I and II) although eight had been incapacitated (Class IV). Remissions occurred within twelve months from beginning of therapy in eleven of the sixteen patients. Remissions continued for one year or longer after the patients were taken off cortisone. In fact, none of the patients in remission had experienced a relapse by the end of the observation period.

It is noteworthy that seven of the sixteen patients who exhibited remission were in the age group between ten and twenty-nine years, the other nine were in the older age group. It will be noted from Table II that the patients in the second and third decade totalled thirteen and the remainder of the series totalled fifty-eight. Whereas the patients from ages ten to twenty-nine made up 18 per cent of the series, they accounted for forty-four per cent of the remissions. The remission rate in the younger age group mentioned was 54 per cent and that in the remainder only 15 per cent. This observation would seem to indicate a significantly better prognosis for patients whose treatment is begun in the second and third decades of life than in those who come under care during the first decade or beyond the age of thirty. (Table VIII.)

Analysis of Cases Exhibiting Slight or No Improvement. In contrast to the sixteen patients who had a remission, thirty-five failed to exhibit

TABLE VIII

ANALYSIS OF SIXTEEN CASES IN REMISSION

Duration of Disease		*Period of Therapy*		*Interval Since Therapy Stopped*	
Less than 6 months	5	One month	3	Still on Cortisone	1*
6–12 months	3	2–6 months	5	Less than one year	0
13–24 months	3	7–12 months	3	12–24 months	11
2–5 years	0	13–24 months	4	25–36 months	3
Above 5 years	5	Over 24 months	1	Over 3 years	1
Stage (before therapy)		*Class* (before therapy)		*Average Daily Maintenance Dose*	
Stage I	6	Class II	4	25–50 mg.	7
Stage II	7	Class III	4	62.5–100 mg.	8
Stage III	3	Class IV	8	125 mg.	1

Age Factor

Age (yr.)	*Remissions*	*No Remissions*	*Total in Series*
0–9	0	3	3
10–19	4	3	7
20–29	3	3	6
30–39	0	7	7
40–49	2	11	13
50–59	6	16	22
60 or above	1	12	13
Total	16	55	71

* This patient presented no evidence of activity but insisted on taking small amounts of cortisone (12.5 mg.) daily.

significant improvement as a result of cortisone therapy. The "favorable" (Table VIII) and "unfavorable" (Table IX) groups differed principally in the stage of the disease at time of therapy and the duration of arthritis before treatment. Whereas 80 per cent of the former group had prolonged cortisone administration on growth of children has not yet been conclusively answered. It is of interest that five of the eight cortisone-treated children were of normal height and four within normal weight range at the end of the observation period. Relapses of arthritis

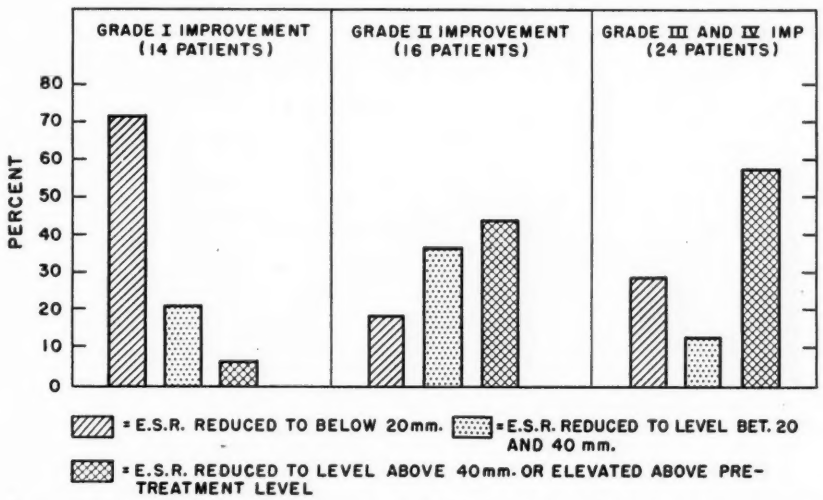


FIG. 5. Relation of extent of reduction in ESR (Westergren) to grade of improvement from cortisone therapy.

reversible arthritis, only 31 per cent of the latter were in this phase and the remainder (69 per cent) in Stage III or IV. (Table IX.) In the "favorable" group 50 per cent had arthritis for less than one year and 31 per cent for longer than five years, whereas in the "unfavorable" group the corresponding percentages were 11 and 63.

Results in Eight Patients with Juvenile Rheumatoid Arthritis. Eight cases of juvenile rheumatoid arthritis are included in this series. The pertinent clinical data and effects of cortisone therapy are listed in Table X. The ages of onset varied from four to thirteen years, the duration of arthritis prior to treatment from ten days to seven years, and the period of cortisone therapy from 223 to 1,210 days. Five of the eight children were totally incapacitated and bedridden before hormone administration was begun. At the end of the observation period all eight patients were ambulatory (one child required the aid of crutches in walking) and attending full sessions at school.

It has been observed by others that children with rheumatoid arthritis usually do not attain normal growth and physical development because of interference with epiphyseal growth. This was true for most of the children in our series at the time they were first admitted for treatment. The question as to the effect of often accompanied by systemic manifestations occurred repeatedly during the course of hormone therapy despite uninterrupted and apparently adequate dosage.

TABLE IX

ANALYSIS OF THIRTY-FIVE CASES EXHIBITING SLIGHT OR NO IMPROVEMENT

(Grade III or IV Response)

Duration of Disease		*Period of Therapy*	
Less than 6 months	2	One month	2
6–12 months	2	2–6 months	9
13–24 months	4	7–12 months	4
2–5 years	5	13–24 months	10
Above 5 years	22	Over 24 months	10
6–10 years	7		
11–15 years	13		
Above 15 years	2		

Stage (before therapy)		*Class* (before therapy)		*Average Daily Maintenance Dose*	
I	5	II	13	25–50 mg	7
II	6	III	15	62.5–100 mg	26
III	16	IV	7	125 mg	2
IV	8				

Erythrocyte Sedimentation Rate. Repeated determinations of sedimentation rate (Westergren) were made in fifty-four patients and the changes compared with clinical results. (Fig. 5.) In ten

TABLE X

RESULTS OF CORTISONE THERAPY IN EIGHT PATIENTS WITH JUVENILE RHEUMATOID ARTHRITIS

Name & Sex	Age at Onset (yr.)	From Onset to Therapy	Stage	Period of Therapy in Days	Average Maintenance Dose (mg./day)	Functional State			Grade Response	Interval Since Stopping Therapy	Weight Before Therapy (lb.)	Weight & Height at Last Observation	Normal Weight & Height (av.)	Relapse during Therapy	Undesirable Effects
						Before Therapy ARA (Class)	At Last Observation ARA (Class)	School Attendance							
D. C. (F)	4	10 days	I (Early)	485	100	BR (4)	AMB (2)	FT	2	Still on therapy	32	44 lb. 41½ in.	38–46 41.5–44.5	Yes	MF (x), AFD, Hir., Acne, Liv. (x)
V. M. (F)	9	9 mo.	II (Moderate)	385	80	BR (4)	AMB (1)	FT	1	2 yr. + 4 mo.	44	112 lb. 63½ in.	92–128 60.5–65	No	MF (x), Diab., Obes., AFD
A. S. (M)	5	12 mo.	II	801	100	BR (4)	AMB (2)	FT	2	Still on therapy	37	95 lb. 54¼ in.	62–84 53–57.5	Yes	MF, Obes.
E. D. (F)	9	18 mo.	II	711	100	AMB (2)	AMB (1)	FT	2	Still on therapy	69	77 lb. 57 in.	82–117 59–64	Yes	MF (x), Hir. (x)
M. B. (F)	13	3 yr.	II	250	75	AMB (3)	AMB (1)	FT	2	Still on therapy	66	93 lb. 58¾ in.	105–136 61.5–66	Yes	MF
P. B. (M)	6	3 yr.	III (Advanced)	1210	50	BR (4)	SA (3)	FT	2	Still on therapy	32	62½ lb. 57¼ in.	78–111 57–63	Yes	MF (x)
V. F. (F)	6	7 yr.	III	223	50	AMB (3)	AMB (1)	FT	2	Still on therapy	82	137½ lb. 61½ in.	105–136 61.5–66	No	MF (x)
T. T. (M)	7	7 yr.	III	399	75	BR (4)	AMB (1)	FT	1	1 yr. + 3 mo.	62	92¼ lb. 61 in.	110–146 64–70	No	MF (x), Hir., Acne (x), Edema

BR = Bedridden
AMB = Ambulatory
SA = Semi-ambulatory

FT = Full-time
MF = Moon face
(x) = Disappeared during continued therapy

AFD = Abnormal fat deposit
Hir. = Hirsutism
Liv. = Liver enlargement

Diab. = Diabetes
Obes. = Obesity

of the fourteen patients (72 per cent) who exhibited remission the ESR was reduced to within normal limits and in three of the remaining four the rate fell but did not quite reach normal values.* In contrast, only three of the sixteen patients (19 per cent) who had Grade II response and seven of the twenty-four patients (29 per cent) with Grade III or IV response were found to have a normal rate. Although there was a general relation between degree of clinical improvement and fall in sedimentation rate, the correlation was limited since several patients who showed Grade I response had a higher sedimentation rate than those who failed to improve significantly.

TABLE XI

BEHAVIOR OF SUBCUTANEOUS NODULES IN FIFTEEN PATIENTS DURING CORTISONE THERAPY

	No. Patients
Premedication nodules disappeared, no new nodules appeared	2
Premedication nodules persisted	8*
New nodules appeared during therapy in patients who had nodules before treatment	8*
New nodules appeared during therapy in patients who did not have nodules before treatment	2

* These two groups overlap, hence the total number of patients listed exceeds fifteen.

Behavior of Subcutaneous Nodules during Cortisone Therapy. Nodules did not disappear during cortisone therapy in the majority of patients who had them prior to treatment. (Table XI.) Two patients in the series developed nodules for the first time while they were taking cortisone and eight patients who had nodules before treatment developed new ones during treatment. The therapeutic response in the fifteen patients with subcutaneous nodules was somewhat less favorable than in those without nodules but the difference was not significant. (It is of interest that none of the ten patients below age eighteen and none of the nine patients with psoriasis had nodules.)

Incidence of Peptic Ulcer. Peptic ulcer occurred in five of the sixty-four patients receiving cortisone. (Table XII.) In four subjects the ulcer was discovered as a result of clinical symptoms and in one an asymptomatic lesion was found by radiography. The latter was the only patient found to have an ulcer among twenty-four who were subjected to routine x-ray studies of the gastrointestinal tract. One gastric and one duodenal perforation occurred among the four patients who presented clinical evidence of ulcer.

TABLE XII

INCIDENCE OF PEPTIC ULCER

	No. Patients
Patients receiving cortisone, routinely x-rayed	24
Detected by x-ray	1
Diagnosed by clinical symptoms (2 cases of perforation)	4*
Total no. with ulcer	5
Total no. of patients observed	64

* One patient gave history of ulcer many years before receiving cortisone. The ulcers developed at following times during cortisone therapy: 23 days, 5 months, 12 months and 16 months. The average daily doses, respectively, were: 125 mg., 175 mg., 110 mg. and 70 mg. Perforations occurred in the first and third of these four cases.

TABLE XIII

DESTRUCTION OF SUBCHONDRAL BONE DURING CORTISONE THERAPY

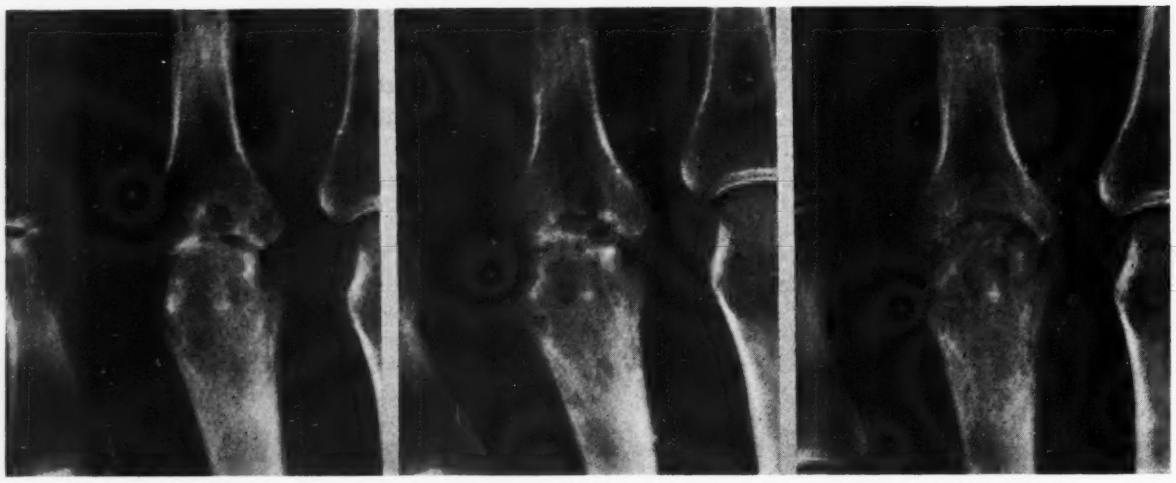
(20 Patients with Serial X-rays)

X-ray Finding	No. of Patients	Duration of Arthritis (Av. in yr.)	Duration of Therapy (Av. in) mo.)	Major & Minor Improvement	Fall in ESR
New areas of destruction appeared	6	2.5	17.5	5	5
Old areas of destruction increased	8	8	26.5	8	7
No increased destruction	5	8	15.5	5	4
Decreased destruction	1	26	12	1	1

The average daily doses of cortisone for the four patients were 175, 125, 110 and 70 mg., respectively. Only one of these four patients was known to have had an ulcer before cortisone. In none of the four were x-ray films taken immediately before administration of cortisone.

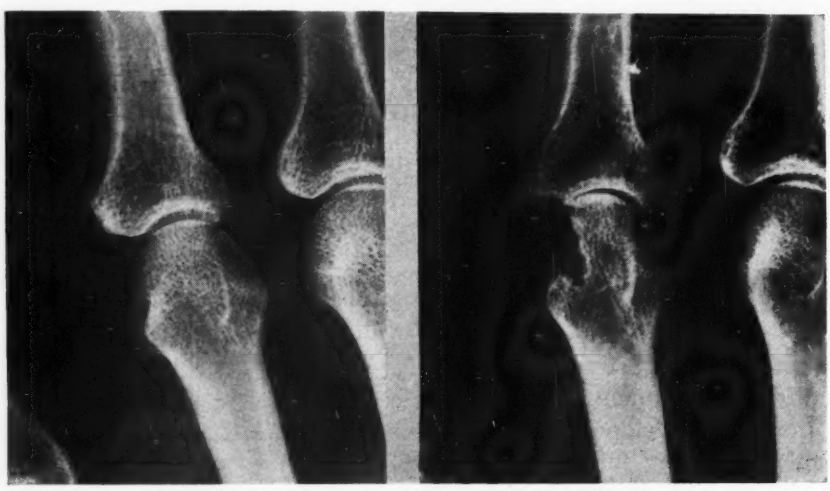
Destructive Changes Occurring during Cortisone Therapy. One of the most important questions which this study aimed to answer was whether cortisone significantly altered the natural course of the disease. Attention was focused on destructive changes in the articular structures. Serial x-ray films were made of involved joints in twenty patients selected at random. Fourteen were found to have had some destruction of the subchondral bone immediately before cortisone was instituted and six had none. (Table XIII.)

* Four of the fourteen patients grouped as Grade I improvement did not have normal sedimentation rates and therefore did not strictly meet all the criteria for this grade required by the American Rheumatism Association classification. They presented, however, no clinical objective or subjective signs or symptoms of activity of the disease.



3/28/50 5/5/52 3/18/53

FIG. 6. Case (V. B.) illustrating increasing destruction of subchondral bone of the second right metacarpophalangeal joint during uninterrupted cortisone therapy. Cortisone was started on March 27, 1950, and continued past March 18, 1953. During this period the patient's arthritis improved clinically and the ESR fell.



3/29/51 11/19/52

FIG. 7. Case (P. R.) illustrating appearance of a new area of bone destruction in the second right metacarpointerphalangeal joint during uninterrupted cortisone therapy. Cortisone was started April 28, 1951, and continued past November 19, 1952. During this period the patient's arthritis improved clinically and the ESR fell.

In the group of fourteen pre-existing areas of destruction increased in dimension in eight patients (Fig. 6), remained essentially unaltered in five and diminished in one. In each of the six patients in the latter group who presented no radiographic evidence of osseous damage prior to cortisone therapy new areas of destruction appeared during cortisone therapy. (Fig. 7.) The mean duration of arthritis before therapy in these six patients was 2.5 years and the mean duration of therapy at the time destructive changes were noted was 17.5 months. It is especially instructive that in five of these six patients there were objective and subjective clinical and also laboratory signs of improvement despite unequivocal radiographic evidence of progression of subchondral bone destruction.

Deaths. Five patients in this series died. (Table XIV.) In three the cause of death was unrelated to cortisone administration; one patient died of carcinoma of the sigmoid colon, another of carcinoma of the transverse colon and a third died of pneumonia which developed three months after a thirteen-day course of cortisone had been discontinued. A fourth patient died at home of cerebral thrombosis at age

seventy-five while receiving cortisone under the care of her private physician. This death possibly may have been related to cortisone therapy. In a fifth patient (A. N.) the cause of death was probably related to hormone therapy. He was first given 100 mg. of cortisone daily for four weeks. The hormone was discontinued because of inadequate improvement. Six weeks later the patient became severely ill and a course of corticotropin (120 mg. daily, intramuscularly) was then instituted. The patient had experienced moderate improvement but suddenly developed fever (106°F.), toxicity and stupor and died within twenty-four hours. Necropsy revealed a confluent, lobular, pneumococcus Type IX pneumonia involving all five lobes. Microscopically, the alveoli contained fibrin, numerous erythrocytes, occasional mononuclear cells and numerous pneumococci. Polymorphonuclear leukocytes were conspicuously scant. The pneumonia had not advanced to hepatization, hence signs of consolidation were absent when the chest was examined one hour antemortem. Other necropsy findings consisted of silicosis, marked hyperplasia of the adrenal cortex (combined weight of both adrenals was 29 gm.) and articular changes typical of rheumatoid arthritis. There was no evidence of necrotizing arteritis, periarteritis nodosa or disseminated lupus erythematosus. The cause of death was a fulminating pneumococcus infection which was clinically masked by corticotropin.

TABLE XIV

DEATHS OF PATIENTS UNDER OBSERVATION

Patient	Age & Sex	Duration of Disease, Pre-treatment (yr.)	Stage	Average Daily Dose (mg. cortisone)	Duration of Treatment	Results of Treatment	Interval from Stopping Cortisone to Death	Cause of Death
E. S.	70, F	1½ yr.	II	100	11 mo.	Grade III*	3 mo.	Cancer of colon
M. H.	48, F	24 yr.	III	75	25 mo.	Grade II	1 mo.	Cancer of colon
I. B.	65, F	27 yr.	IV	50	13 days	Grade III	3 mo.	Pneumonia
S. S.	75, F	2 yr.	III	50	34 days	Grade III	None	Cerebral thrombosis
A. N.	49, M	11 yr.	IV	100	61 days	Grade IV	Corticotropin (see text)	Pneumonia

* Grade of improvement according to criteria of American Rheumatism Association.

Undesired Effects of Cortisone. Observations on side effects were made on fifty-nine patients in the series; thirty-two females and twenty-seven males. Twenty-seven females (84 per cent) and nineteen males (70 per cent) manifested one or more such signs. (Table XV.) The effects that were especially more common among women than men were hirsutism, abnormal fat deposits, bone fractures and mental depression. The incidence of side effects was related to cumulative amounts of cortisone taken. It is interesting that many side effects disappeared despite continued hormone therapy and that the disappearance rate was relatively higher among females than males. All the symptoms listed were reversible upon discontinuance of the steroid except, of course, fracture and perforated peptic ulcer. The four women in whom bone fractures occurred were in the postmenopausal period; cortisone had been discontinued in two at the time fracture occurred. Elsewhere the authors have reported in greater detail edema, hepatomegaly and diabetes associated with prolonged hormone administration.[2–5]

COMMENT

Observation of this group of patients has afforded the authors an opportunity to study the metabolic and clinical effects of adrenal cortical steroids. Some of these investigations have been previously reported.[6–9] In this paper an attempt has been made to evaluate the usefulness of

cortisone as a therapeutic agent in rheumatoid arthritis and to determine its influence on the natural course of the disease.

We have been impressed with the complexity and difficulty of this task and with the pitfalls that beset the interpretation of data collected for this purpose. It should be emphasized that certain factors inherent in the sampling of patients may influence and indeed bias one's results. It is clear that the *apparent* beneficial effects of any compound to be tested in this disease will be enhanced by the proportion of patients (1) who have had the disease for less than one year, (2) who have reversible pathologic changes in the joints, (3) whose disease is still active, (4) whose arthritis is not severe and (5) whose treatment was begun during adolescence or early adult life. The physician may include in his management auxiliary measures such as bed rest, corrective exercises, physical therapy, application of casts or splints and customary drugs such as aspirin. By his demeanor, moreover, the clinician may convey a certain optimism, interest and solicitude which fortify the patient with new hope. These medical, physical and psychologic factors may contribute substantially to the patient's improvement yet are often ignored as adjuvants when a specific drug, administered concomitantly, is being assayed.

TABLE XV

INCIDENCE OF SIDE EFFECTS AND COMPLICATIONS IN FIFTY-NINE PATIENTS RECEIVING PROLONGED CORTISONE THERAPY*

	No. of Patients Manifesting Effects	Females	Males	Disappearance of Effects during Continued Administration	
				Females	Males
Moon face	31	21	10	12	1
Edema	16	10	6	4	4
Hirsutism	13	10	3	2	0
Abnormal fat deposit	7	6	1	0	0
Acne	5	3	2	3	2
Amenorrhea	5	5	..	0	..
Peptic ulcer	5	2	3	1	0
Fracture	4	4	0	0	0
Mental depression	4	4	0	1	0
Flushing of face	4	2	2	1	0
Adrenal cortical insufficiency	3	2	1	0	0
Hypertension	3	2	1	0	0
Weakness	3	3	0	0	0
Skin rash	3	2	1	2	0
Paresthesias	3	3	0	1	0
Hepatomegaly	2	2	0	1	0
Pigmentation	2	2	0	0	0
Headache	2	1	1	1	0
Cutaneous purpura	2	2	0	1	0
Diabetes	1	1	0	0	0
Abdominal distention	1	1	0	1	0
Dry scaly skin	1	1	0	1	0

* This group consisted of thirty-two females and twenty-seven males; five females and eight males experienced no side effects.

How objective is the measurement of increase in the functional capacity of the rheumatoid patient? Motivation of the patient, relief from pain by analgesics, temporary joint immobilization or other accessory measures may contribute greatly toward grading of the patient. Difficulty in distinguishing true antirheumatic effects from influences due to emotional factors is further increased when the clinical trial involves an agent which itself has the capacity to elicit definite psychologic responses. It has been recognized by many observers that cortisone

induces a sense of well being, an emotional "lift," increased confidence and a greater capacity to help oneself. Unquestionably, these psychologic factors resulting from hormonal administration can increase a patient's ability to do work apart from other contributory factors such as subsidence or suppression of inflammation in articular structures, improved muscular coordination or lessened pain. In grading the response to cortisone, therefore, much reliance has been placed by the authors on objective measurements such as degree of periarticular swelling or intra-articular effusion, range of joint motion, warmth of the surface of the joint, tenderness on pressure and change in muscular mass, power and coordination.

In determining the influence of cortisone on the natural course of rheumatoid arthritis special attention was directed to (1) appearance of new or spread of old areas of destruction in the articular structures as seen by x-ray, (2) extension of the disease process clinically to involve previously unaffected joints, (3) appearance of new or persistence of pre-existing subcutaneous nodules, (4) development of deformities and (5) incidence, promptness and duration of remission

Serial x-ray films of clinically affected joints, including radiograms made immediately before and after treatment, were obtained in twenty patients. In 70 per cent cortisone failed to halt the extension of subchondral bone destruction or prevent the appearance of new osseous erosion. Yet almost all these patients were considered to have benefited markedly or moderately from hormone therapy when assayed by conventional clinical or laboratory standards. We consider this conclusive evidence that in these subjects progression of the joint disease was not arrested by cortisone; however, we do not know what the course would have been without cortisone.

In thirteen or 20 per cent of the sixty-four patients who were observed without interruption, joints that were previously unaffected were attacked while cortisone was being administered in apparently adequate doses.

Subcutaneous nodules often disappear spontaneously; on the other hand, they may sometimes persist even after apparently complete clinical remission. Disappearance or persistence of subcutaneous nodules therefore may not be reliable indices of the effect of a given agent on the disease process. The appearance of new granulomas, however, in patients receiving treatment should constitute evidence, we believe, that the test agent lacks the capacity to arrest the progression of the disease.

Clinical remissions in rheumatoid arthritis have been reported to occur in from 15 to 32 per cent of subjects treated by "conservative" measures, exclusive of gold or hormone therapy.[10,11] The remission rate of 23 per cent in our series therefore may not indicate a significant effect of cortisone on rheumatoid arthritis. It should be noted, however, that remission in all our cases occurred within the first twelve months of treatment, in some cases within six weeks, and lasted uninterruptedly until the end of the observation period. All other patients who were not in remission, however, experienced exacerbation of the arthritis when cortisone was discontinued.

The relative promptness and high incidence of improvement with cortisone was striking. Only 6 per cent of the subjects failed to derive any benefit from the hormone. Throughout the entire period of study at least 50 per cent, and at certain periods 75 per cent, of the patients exhibited either complete remission or marked improvement. (Fig. 2.) The "salvage" rate achieved by cortisone therapy is especially impressive in the patients who were totally incapacitated or unemployable when treatment was started. Eighty per cent became self-sufficient and employable when cortisone was administered. In approximately half the total number of patients in this series improvement was not great enough to warrant the risks implicit in long-term cortisone administration.

SUMMARY

In this report are presented the data collected from observation over a four-year period of seventy-eight patients with rheumatoid arthritis (including nine cases of juvenile rheumatoid arthritis) who were treated with cortisone for intervals varying from a few weeks to almost four years. The patients were examined every four weeks or more frequently.

The results have been analyzed to yield information concerning the following: composition of the group according to certain clinical features of rheumatoid arthritis; age and sex distribution; duration and stage of arthritis; duration of cortisone therapy; average daily maintenance dose; functional improvement as measured by four different criteria; relation of

duration of therapy to grade of therapeutic response; comparison of certain factors in the groups that exhibited Grade I and Grade III or IV response; behavior of subcutaneous nodules during therapy; appearance or extension of bone destruction despite maintenance therapy and good clinical response; occurrence of undesirable effects including peptic ulcers, fractures and one death from overwhelming sepsis.

An attempt is made to determine what effect, if any, cortisone exercises on the natural course of rheumatoid arthritis.

The factors which may inadvertently influence or even prejudice results achieved by an agent subjected to clinical trial in this disease are discussed.

CONCLUSIONS

In properly selected cases of rheumatoid arthritis adrenal cortical steroids such as cortisone or hydrocortisone are very useful agents. The patients most suitable for hormone administration are those whose disease is severe, reversible, of relatively recent development but following a rapidly progressive, relentless course. It may also be useful in patients who have not responded well to or are unable to tolerate other antirheumatic drugs. Patients who do not require larger than moderate doses of steroid for the control of their arthritis and who present no contraindications or unusual susceptibility to the side effects of the hormone are suitable subjects for steroid therapy. It is clear that many patients can tolerate maintenance doses of cortisone for several years without becoming refractory and without developing clinical symptoms of adrenal cortical insufficiency.

The impressive assets of these hormones consist of a high rate of therapeutic response especially in the first few months of treatment, relatively early recovery of good functional capacity with restoration to employability and self-sufficiency and aid in implementation of an effective rehabilitation program. Most of the undesirable side effects are reversible; in fact, many disappear even during continued administration.

Certain limitations of steroid therapy have become apparent during this study. These consist of failure appreciably to alter or arrest the extension of the pathologic processes of the disease; the frequent occurrence of relapses, at times quite severe, when the drug is discontinued; and the development in some cases of serious complications or side effects of prolonged cortisone therapy.

Acknowledgment: It is a pleasure to acknowledge with gratitude the efforts of the following Fellows who participated in observation and study of patients in this series: B. Appel, E. Dresner, G. Fearnley, D. Ford, J. Glyn, A. J. Kaltman and E. Scull. The authors are especially indebted to Mrs. Charlotte Stern without whose perseverence in maintaining accurate follow-up records this analysis could not be made.

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Effect of Cortisone in the Long-term Treatment of Rheumatoid Arthritis*

Observation of Thirty-five Patients over a Three-year Period

ELAM C. TOONE, JR., M.D. *and* ROBERT IRBY, M.D.†
Richmond, Virginia

FOLLOWING the introduction of cortisone as an antirheumatic agent by Hench, Kendall, Slocumb and Polley in 1949,[1] it soon became evident that treatment of rheumatoid arthritis with this drug would fall into two phases.[2,3] The first of these was the period of intensive treatment during which the disease was brought under control with relatively large doses of cortisone. The second phase was that of maintenance management, during which an attempt was made to hold the symptoms of the disease under control and at the same time prevent the development of adverse reactions. This second phase was the most important and at the same time the most difficult part of the regimen. Unless it could be carried out successfully, with continued antirheumatic effect on the one hand and minimal toxic reactions on the other, the practical value of this hormone in the control of rheumatoid arthritis would be seriously limited. There have been many excellent reports published on the results of the treatment of rheumatoid arthritis with cortisone over short periods of time varying from a few weeks to two years.[2–10] However, there have been relatively few dealing with the continuous use of cortisone for periods of three years or more.[11]

MATERIAL AND METHOD

This report will deal with the clinical course of thirty-five patients with rheumatoid arthritis who were started on cortisone therapy during the summer of 1950 and continued under observation until the summer of 1953. Particular emphasis will be placed on the eleven patients who have taken the drug for three years, and on the five deaths which occurred during the period of observation. (Fig. 1.)

Thirty cases had peripheral joint involvement, five had rheumatoid spondylitis. There were nineteen males and sixteen females. The ages varied from thirty-three to seventy-four years. In fourteen cases the disease had existed for less than five years, in eight from six to ten years and in thirteen for more than ten years. The group represented the disease in varying stages of severity although the greater number showed advanced structural changes and functional incapacity. There were two cases classified as Stage I, seven as Stage II, six as Stage III and twenty as Stage IV. As would be expected, those patients classified as Stage III or IV had had the disease for a longer period of time, although there were some notable exceptions. (Table I.)

TABLE I
CLASSIFICATION OF SEVERITY

Structure		Function	
Stage I	2	Class I	1
Stage II	7	Class II	3
Stage III	6	Class III	16
Stage IV	20	Class IV	15
	35		35

A number had complications or associated clinical conditions of significance. Psoriasis was present in one case. Another had an enlarged liver and spleen but never showed evidence of leukopenia and was only tentatively classified as Felty's syndrome. Two cases showed evi-

* From the Department of Medicine, Medical College of Virginia Hospitals, Richmond, Va.
† Trainee, National Institute of Arthritis and Metabolic Diseases.

dence of right bundle branch block in the electrocardiogram but had no other evidence of cardiovascular disease. One had a moderate hypertension and one had an old right hemiplegia without hypertension. Early portal cirrhosis was present in one case. Of special interest was one case of exophthalmic ophthalmoplegia without evidence of hyperthyroidism. One case was later diagnosed by skin biopsy as scleroderma and should not have been included in the group.

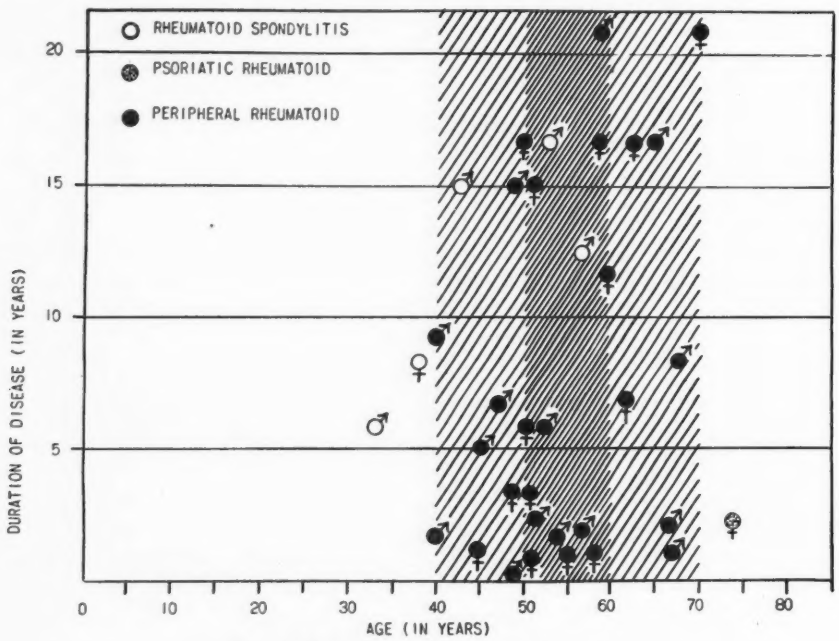

FIG. 1. Data on patients investigated.

All patients were hospitalized at the beginning of the treatment program. In addition to a detailed history and physical examination, the following laboratory and special studies were carried out: routine blood count, urinalysis, serologic tests, erythrocyte sedimentation rate, fasting blood sugar, blood electrolytes, total and fractional serum proteins, and in some instances a blood cholesterol. X-ray examinations were made of the chest and of typical joint areas. The diagnosis was confirmed in two cases by biopsy of a rheumatoid nodule from the arm, and in one case by biopsy of the synovial membrane from the knee.

During the period of hospitalization of from ten to fourteen days intensive treatment with intramuscular injections was carried out. In thirty-four cases the immediate response was gratifying. There was striking relief of pain, improvement of muscle stiffness and in some instances a surprising increase in joint motion. Most patients enjoyed a mild euphoria, increase in appetite, and gain in weight and energy. The remaining patient died during the initial treatment period.

Before leaving the hospital the patients were carefully advised that cortisone was not curative but exerted only a controlling influence over the disease, and that treatment would have to be continued indefinitely. They were instructed to keep in close contact with their physicians so that the proper maintenance dose could be arranged. They were likewise cautioned about possible toxic reactions such as sudden weight gain, ankle edema, excitement or insomnia, extreme weakness, the appearance of hair on the cheeks or around the lips, fullness of the face and the development of hypertension or diabetes.

Maintenance Management. At the end of one year all patients were sent a questionnaire and at the end of two and three years, respectively, those patients who were still taking cortisone were contacted. The daily maintenance dose of cortisone varied considerably within the group. Since in its natural course rheumatoid arthritis is prone to go through periods of remission and exacerbation, the maintenance schedule often had to be altered in individual patients from time to time. The average, however, had been 75 mg. given in divided doses of 25 mg. each with a range from 50 to 150 mg. daily. (Table II.)

The therapeutic criteria used were those advocated by the American Rheumatism Association[12] but modified somewhat due to the fact that much of the information was obtained by questionnaire and represented more information based on subjective response rather than objective signs of improvement. Grade I indicated a complete remission, Grade II major improvement, Grade III minor improvement and Grade IV failure. There was no indication that any of the patients treated underwent complete remission and therefore no Grade I response was recorded.

TABLE II
DAILY MAINTENANCE DOSE

Cortisone (mg.)	12 Months	24 Months	36 Months
125–150	2	1	0
100	7	2	3
75	8	5	4
50	2	5	4
Cases	19	13	11

TABLE III
RESULTS

	12 Months	24 Months	36 Months
Grade I (complete remission)	0	0	0
Grade II (major improvement)	7	8	7
Grade III (minor improvement)	12	5	4
	19	13	11
	Drug Stopped		
Grade IV (failure)	16	6	2

At the end of twelve months nineteen patients were still taking cortisone. Seven had experienced major improvement and were classified as Grade II response; twelve had experienced minor improvement and were classified as Grade III; sixteen patients had discontinued the drug and were considered failures, or a Grade IV response. Of these 16 patients seven had discontinued treatment because cortisone had not controlled the symptoms of the disease adequately, and were considered treatment failures; nine had discontinued the drug because of the development of toxic reactions, and were considered failures due to toxicity. There were two deaths during this period.

At the end of twenty-four months thirteen patients were still taking cortisone. Eight were classified as Grade II response and five as Grade III. Six additional patients had discontinued the drug, three because of treatment failure and three because of toxicity. There were three deaths during this period.

TABLE IV
ANALYSIS OF GRADE IV FAILURES

	12 Months	24 Months	36 Months
Treatment	7	3	1
Toxic	9	3	1
Deaths	2*	3	0

* One under Px six months; death eighteen months later.

At the end of thirty-six months eleven patients were still on cortisone therapy; seven were considered as Grade II response and four as Grade III. Two patients had discontinued the drug, one because of treatment failure and one because of toxicity. There were no deaths in this period. (Tables III and IV.)

CASE REPORTS OF PATIENTS TAKING CORTISONE AT THE END OF 36 MONTHS

CASE I. C. W., a seventy-nine year old white female, had Class IV, Stage IV psoriatic rheumatoid arthritis of five years' duration. The average daily dose of cortisone was 67½ mg. At the onset of treatment the patient had been completely bedridden and in constant pain requiring narcotics in small doses. The use of cortisone made her comfortable at all times, enabled her to get about her living quarters satisfactorily in a wheel chair and to take automobile trips. Adverse reactions consisted of a weight gain from 115 to 135 pounds, a moon face, moderate euphoria and dependent edema which was controlled by a low sodium diet. The functional capacity improved from a Class IV to a Class III. (Grade II—major improvement.)

CASE II. H. E., a fifty-four year old white male, had Class III, Stage II rheumatoid arthritis of two years' duration. The average daily dose of cortisone was 87½ mg. but on occasion was increased to as much as 150 mg. to meet transient

exacerbations. According to his evaluation, the drug had relieved pain and stiffness by 50 per cent and there was a notable decrease in joint swelling and an improvement in the range of motion. Adverse reactions consisted of an abscess of the buttocks during the period in which cortisone was administered intramuscularly, transient edema, a severe upper respiratory infection and retinal vein thrombosis. There had been no significant weight gain. The functional capacity improved from Class III to Class I. (Grade II—major improvement.)

CASE III. H. W., a thirty-eight year old female, had Class IV, Stage IV rheumatoid spondylitis with peripheral joint involvement of ten years' duration. The rheumatoid arthritis was complicated by residual deformities of poliomyelitis. The average daily dose of cortisone was 100 mg. At the time treatment was begun she was confined to bed or a wheel chair but since then she has been able to walk with the help of a cane and take automobile rides. According to her evaluation, pain and stiffness were relieved 50 per cent. Adverse reactions included a weight gain from 130 to 156 pounds, a moon face and a moderate elevation of the blood pressure from 110/68 to 150/112. The functional capacity improved from Class IV to Class III. (Grade II—major improvement.)

CASE IV. L. G. a fifty-six year old male, had Stage II, Class III rheumatoid arthritis of two years' duration. The average daily dose of cortisone was 50 mg. At the onset of treatment activities were confined to a few steps in the bedroom and these were carried out with considerable pain. He was completely unable to follow his profession as a trial lawyer. There has been a 75 per cent improvement in pain and stiffness, and he is now able to work regularly. A severe attack of herpes zoster of the ophthalmic branch of the fifth nerve occurred during the treatment period. The functional capacity improved from Class III to Class I. (Grade II—major improvement.)

CASE V. V. C., a forty-six year old male, had Stage II, Class III rheumatoid arthritis of eighteen months' duration. The average daily dose of cortisone was 75 mg., increased on occasion to 150 or 200 mg. in order to combat transient exacerbations. Prior to the onset of treatment he was in constant severe pain and was unable to work as a dental technician more than 50 per cent of the time. His walking and standing were limited to a bare minimum. On treatment with cortisone he has indicated 75 per cent improvement in pain and stiffness, has been able to work regularly and now plays tournament golf. The only adverse reaction was a buttock abscess. The functional capacity improved from Class III to Class I. (Grade II—major improvement.)

CASE VI. B. G., a fifty-one year old female, had Stage II, Class II rheumatoid arthritis of seven years' duration. The average daily dose of cortisone was 100 mg. She was in constant pain, unable to attend to her household duties, and the disease was so progressive as to indicate the development of completely crippling disability within a short period. There were 50 per cent relief of pain and 25 per cent relief of joint stiffness. The joint swelling improved 75 per cent. She can now carry on her household work satisfactorily. There has been a weight gain from 185 to 195 pounds. For a period she developed a painful tongue without demonstrable cause and with no significant objective change. The functional capacity improved from Class II to Class I. (Grade II—major improvement.)

CASE VII. E. F., a male aged forty-five years, had Stage IV, Class III rheumatoid spondylitis of fifteen years' duration. He had been able to work regularly as a contractor but was unable to climb ladders, suffered pain constantly and his rest was greatly disturbed. The average daily dose of cortisone was 75 mg. On treatment there was 75 per cent improvement in pain. There was no increase in chest expansion or range of back movement but he became able to do any type of job except one that required heavy lifting or stooping. There was a weight gain from 135 to 142 pounds, but no adverse reactions. The functional capacity improved from Class III to Class I. (Grade II—major improvement.)

CASE VIII. W. M., a sixty year old male, had Stage IV, Class IV rheumatoid arthritis of twenty-five years' duration. The average daily dose of cortisone was 100 mg. He had been completely incapacitated prior to treatment and unable to attend to his profession as a lawyer. There was 50 per cent improvement in pain and stiffness, and he was able to return to part-time work. At the onset of treatment an enlarged spleen and liver without leukopenia were noted. There was no aggravation of this condition. An abscess of the buttocks was the only adverse reaction. The functional capacity improved from Class IV to Class III. (Grade III—minor improvement.)

CASE IX. M. H., a female age fifty years, had Stage IV, Class IV rheumatoid arthritis of twenty

years' duration. The average daily dose of cortisone was 67½ mg. Prior to treatment she had been completely bedridden. On treatment there was a 50 per cent improvement in pain and 25 per cent improvement in stiffness. She became able to entertain at dinner parties and to take automobile trips. A small decubitus ulcer healed promptly after ambulation was instituted. Between the second and third years of treatment she fell and fractured her hip, and has been a semi-invalid since. There was a weight gain from 70 to 83 pounds, and a rise in blood pressure from 135/70 to 178/90. The functional capacity improved from Class IV to Class III. (Grade III—minor improvement.)

CASE X. F. W., a fifty-one year old female, had Stage IV, Class IV rheumatoid arthritis of seven years' duration. The average daily dose of cortisone varied from 50 to 75 mg. Prior to treatment she had been confined to bed but since then has been up and about the house and able to take care of light household duties. She continued to have considerable pain and difficulty with her feet, due in part to a weight gain from 114 to 150 pounds. A moon face developed, and on one occasion a moderate degree of nervousness and irritability. The functional capacity improved from Class IV to Class III. (Grade III—minor improvement.)

CASE XI. M. P., a fifty year old female, had Class IV, Stage IV rheumatoid arthritis of twenty years' duration. Prior to treatment she had suffered a great deal of pain and had been confined either to bed or a wheel chair. On cortisone treatment she noted 50 per cent improvement in pain but obtained no improvement in the functional capacity of her joints. The average daily dose of cortisone was 50 mg. Adverse reactions consisted of a buttock abscess, ankle edema, moon face, multiple petechiae around the ankles, and on one occasion an acute flare-up of a skin disease diagnosed as psoriasis. The weight gain was from 140 to 164 pounds. The functional status remained unchanged. (Grade III—minor improvement.)

ANALYSIS OF DEATHS

Five deaths occurred among the original thirty-five patients chosen for cortisone therapy in the thirty-six months' observation period. Of these one died twenty months after cortisone therapy had been discontinued but the other four were still either under treatment or symptoms of the final illness developed during the period of cortisone administration.

Patient E. B., a seventy year old female, had Stage IV, Class IV rheumatoid arthritis of fifteen years' duration. In addition she had a compensated cardiac disease characterized by auricular fibrillation which was originally thought to be due to arteriosclerosis. The daily maintenance dose of cortisone was 50 mg. from July, 1950, to January, 1951, for a total treatment period of six months. At the end of this period a confused mental state developed and she was re-admitted to the hospital. There was some question as to the cause of this psychosis and consideration was given to cerebral arteriosclerosis, cerebral emboli or cortisone toxicity. It was believed that the cortisone should be discontinued. The mental confusion disappeared but the patient remained quite depressed after the drug was discontinued and there was a relapse of her arthritic state. Death occurred August 2, 1952, twenty-five months after cortisone therapy had been initiated and eighteen months after the drug had been discontinued. Postmortem examination showed an old rheumatic mitral stenosis and multiple emboli to the brain, kidneys and spleen. The adrenal glands were found to be normal on gross and microscopic examination.

Patient J. F., a sixty-two year old female, had Stage IV, Class IV rheumatoid arthritis of eight years' duration. She had not been considered a satisfactory candidate for treatment, due to the advanced nature of the disease, malnutrition and renal damage thought to be the result of vitamin D intoxication, but the family was most insistent that the drug be tried. After receiving a total of 1,700 mg. of cortisone and on the twenty-sixth day of treatment, a severe gastrointestinal upset characterized by nausea and vomiting developed, and the drug was discontinued. After two days the gastrointestinal symptoms subsided and the clinical picture appeared to have improved generally. On the afternoon of the fourth day following the withdrawal of cortisone, she suddenly developed severe pain in the left lower quadrant of the abdomen associated with abdominal rigidity, temperature elevation to 103°F., leukocytosis and profound circulatory collapse. Electrolyte studies recorded at the time were normal. No postmortem examination was allowed but clinically it was thought that an acute peritonitis

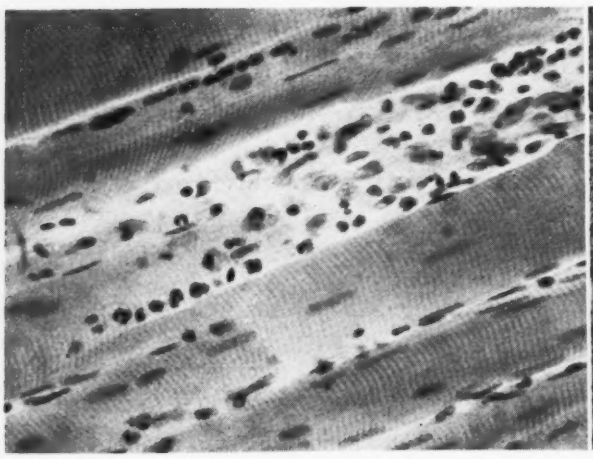

FIG. 2. Case v. Photomicrograph of myocardium; × 400.

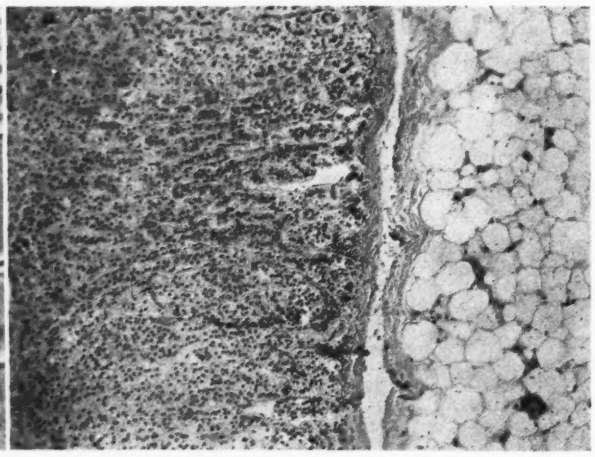

FIG. 3. Case v. Photomicrograph of adrenal gland; × 150.

had developed, possibly from a ruptured diverticulum.

Patient E. S., a fifty year old female with Stage IV, Class IV rheumatoid arthritis of four years' duration, was started on cortisone in June, 1950, and thereafter maintained on an average daily dose of 100 mg. until her death twenty months later. Fourteen months after treatment had been started the patient fell and fractured her hip. Two months later an unusual clinical state developed which, as described by her local physician, was characterized by acute episodes of back and abdominal pain usually lasting for one week, recurring at intervals of from four to six weeks, and extending over a period of four months. During the episodes of acute pain large doses of narcotics were required to give relief. There was a temperature elevation to 108°F. just prior to death and, according to reports received, the electrocardiogram, chest x-ray, blood electrolytes and blood sugar were normal. No postmortem examination was made and no clinical opinion ventured by her attending physician during the terminal illness. It is possible that this patient may have suffered multiple compression fractures of the vertebrae although the cause of death remains obscure.

Patient E. W., a seventy-two year old female with Stage IV, Class IV rheumatoid arthritis of thirty years' duration, was started on cortisone therapy in August, 1950, and maintained on an average daily dose of 50 mg. until April 1, 1952, for a total period of twenty months. At this time she was hospitalized because of the development of acute right upper quadrant pain associated with temperature elevation. The pain disappeared and the temperature elevation subsided under antibiotic therapy. It was believed that she had a subsiding cholecystitis. The patient suffered a generalized convulsion during her hospital stay which was largely unexplained and did not recur. The occasion was taken to compare her electrocardiogram, blood sugar and electrolytes with those made before the initiation of cortisone therapy, and all were found to be normal and unchanged in character. The other laboratory studies were normal. Because of the patient's age and the severe nature of the rheumatoid arthritis no serious consideration was given to surgical intervention. Death occurred at home two weeks after hospitalization and followed another episode of acute abdominal pain. No postmortem examination was carried out but the clinical impression was that she probably had had a recurrence of the acute cholecystitis with rupture of the gallbladder.

Patient R. B., a fifty year old male with Stage IV, Class IV rheumatoid arthritis of ten years' duration, was started on cortisone in August, 1950. The usual daily maintenance dose was 100 mg. with an occasional increase to 200 mg. because of relapses. This was continued until April, 1952, twenty months after treatment had been started. At this time ankle edema became marked, shortness of breath developed, and it became increasingly difficult to control the symptoms of his disease even with doses of cortisone of 200 mg. daily. He was hospitalized, the cortisone withdrawn and treatment with corticotropin initiated. Edema and shortness of breath continued and this drug was discontinued after a brief period. Following this his joint symp-

toms became much intensified, large doses of narcotics were necessary to control discomfort and the development of severe nausea and vomiting necessitated hospitalization again. The downhill course thereafter was rapid and progressive. Death occurred twenty-four months after treatment with cortisone had been begun and four months after the drug had been discontinued. The clinical impression of the attending physician at the time was that death had occurred from congestive heart failure and "cortisone toxicity."

A postmortem examination was carried out with gross findings showing advanced rheumatoid arthritis, nephritis, congestion of the lungs, liver and spleen, a flabby heart and pericardial adhesions. The microscopic examination was reported as follows: "Sections of the myocardium showed infiltration with eosinophilic and neutrophilic granulocytes accompanied by lymphocytes which predominated the cellular picture. There was loss of striation in the muscle fibers of the affected areas. The process in the myocardium was diffuse. It was considered compatible with the myocarditis seen in a variety of collagen, vascular, or hypersensitivity diseases." (Fig. 2.) Sections of the adrenals showed the capsule to be thickened and the zona glomerulosa to be indistinct. There was some loss of lipoid in the fasiculata layer. The most significant change appeared to be a diminution in the width of the cortex rather than any specific cellular change. (Fig. 3.)

MAJOR ADVERSE REACTIONS

Toxic reactions of a major character, not including fatalities, occurred in ten instances and were sufficiently severe to necessitate discontinuance of treatment.

Psychosis.[13,14] Three cases developed a disturbed mental state. One maniacal psychosis required electro shock therapy but made a complete recovery and returned to his previous occupation as a druggist. The second case was a female who was ultimately diagnosed as scleroderma, and who developed paranoid ideas with elements of hysteria. Her mental state improved after cortisone was discontinued. The third developed a severe depression with mild confusion and disorientation. She made a gradual recovery after withdrawal of cortisone. There always remained some question as to whether this mental upset was due to the cortisone or to emboli coming from a fibrillating auricle.

Edema.[15,16] Two patients developed definite fluid retention and edema. One of these showed mild pulmonary congestion. Both cases showed prompt disappearance of the edema when placed on a low sodium diet and when the dose of cortisone was reduced. In one of the cases this was quite dramatic, with loss of 7 pounds in body weight over a period of three days. The edema returned in both instances when the dose of cortisone was increased sufficiently to control the arthritic symptoms, and treatment ultimately had to be discontinued.

Leukopenia.[17] One patient developed leukopenia and granulocytopenia. Prior to the use of cortisone the white blood cell count was 5,690 with a polymorphoneutrophil differential of 45 per cent. During the ninth week of treatment the leukocyte count dropped to 2,500 with a polymorphoneutrophil differential of 8 per cent. A sternal marrow puncture showed depression of the myeloid elements but no disturbance of the erythroid series. Over a period of three months there was no substantial change in the leukocyte or differential count. At the end of this time oral cortisone was given, and after three weeks the white blood cell count was reported as 4,650 with 67 per cent polymorphoneutrophils. Since the blood picture had returned to normal on treatment with cortisone acetate, it was believed that probably one of the vehicles of the intramuscular preparation was responsible.

Exophthalmos. One patient had a unilateral exophthalmos and a concomitant paralysis of the superior oblique muscle without evidence of hyperthyroidism. An increase of the exophthalmos was noted while on cortisone therapy. It was not known for certain if cortisone aggravated the condition but the drug was discontinued. Following this the exophthalmos receded but the muscle paralysis continued and diplopia was still present. The rheumatoid arthritis has remained in remission induced by chrysotherapy and phenylbutazone.

Gastrointestinal Bleeding.[15] There was one case of massive gastrointestinal bleeding which was thought to have originated either from a hiatus hernia or a diverticulum of the duodenum. Cortisone was discontinued and treatment with this drug was not attempted again.

Hypertension.[18] Hypertension developed to such a serious degree in one patient after two years of cortisone treatment that the drug had to be discontinued. At the onset of the treatment period the blood pressure was recorded as 180

systolic and 110 diastolic. Gradually it rose, reaching a height of 260 systolic and 200 diastolic. The patient never showed clinical evidence of cardiac, cerebral or renal disturbance. (Table v.)

TABLE V
MAJOR TOXIC REACTIONS

	12 Months	24 Months	36 Months
Fatality	2	3	0
Psychosis	3	0	0
Edema	2	1	0
Leukopenia	1	0	0
Exophthalmos	1	0	0
Gastrointestinal bleeding	1	0	0
Hypertension	0	0	1
Total	10	4	1

Miscellaneous and Associated Reactions.[13–16,18–20] The most consistent side reaction noted during cortisone therapy was the development of euphoria, often associated with an increase in appetite and energy, during the period of intensive treatment, and usually subsiding on the reduced dose of the maintenance regimen. Mild androgenic effects were frequently encountered and were manifest by moon face in eight cases, hirsutism in three, and a buffalo hump in one. Acne was noted only occasionally. Ecchymotic areas developed around the ankles in three cases. Peptic ulcer symptoms became evident in two cases but were not sufficiently severe to warrant stopping treatment. Hypertension of a moderately severe nature developed in two cases but treatment was continued.

Two patients fractured hips following severe falls but showed no evidence of unusual osteoporosis. Two cases developed herpes zoster although a recent report[20] indicates that cortisone was beneficial in the treatment of this condition. Two patients complained of a sore tongue lasting for several months, subsiding spontaneously, and never showing any significant physical changes. Thrombosis of a central retinal vein occurred in one case but treatment was not discontinued.

The two patients with bundle branch block showed no other signs of cardiac disease and the electrocardiographic changes remained stable. The patient with portal cirrhosis developed no complication.

There was no evidence that any of the patients developed active pulmonary tuberculosis, diabetes mellitus, significant potassium deficit, adrenal failure under stress or delayed wound healing. (Table VI.)

TABLE VI
MINOR AND ASSOCIATED REACTIONS* NOT NECESSITATING WITHDRAWAL OF CORTISONE

Reaction	No.
Fractured hip	2
Hypertension	1
Abscess of buttock	6
Shingles	2
Sore tongue	2
Progressive joint damage (rapid)	2
Thrombosis central retinal vein	1
Peptic ulcer symptoms	2

* Frequently encountered: Weight gain, euphoria, mild edema, moon face, hirsutism, petechiae; not encountered: tuberculosis, diabetes, delayed wound healing, evidence of adrenal failure under stress.

COMMENT

The management of thirty-five patients with rheumatoid arthritis by means of cortisone over a period of three years has presented a number of complex problems. The beneficial results have been limited. The group, however, was represented by a large number of long-standing and advanced cases of rheumatoid arthritis; many of the patients were elderly and in poor general health.

Only eleven of the original thirty-five (31.1 per cent) were still under treatment at the end of the period of observation. None obtained a complete remission and all were dependent on continued use of cortisone. In the seven cases classified as a Grade II response continued use of the drug seemed indicated because of the degree of comfort obtained, the increase in the functional capacity and the ability in some instances to earn a livelihood. In the four cases with a Grade III response, however, it is doubtful that continued use of the drug was justified since similar results might have been obtained by more conservative measures.

The five deaths occurring during the period of observation were disturbing. This, however, may have been greatly influenced by the severity and duration of the disease, and the general physical conditions and ages of the patients. No deaths have been observed in an additional

group of fifty cases treated with cortisone over a shorter period of time. Unfortunately, postmortem examinations were made in only two cases. The deaths in three instances occurred in their local communities, or under the observation of the local physicians, and more complete and exact data were not obtained. In the two cases in whom postmortem examinations were obtained, death occurred in one instance from multiple emboli to the brain, lungs and kidneys eighteen months after cortisone had been discontinued, and it could hardly have been a factor in causing death. The other was thought to have died in an acute rheumatoid state which developed while on active cortisone treatment, with widespread vascular and serous membrane lesions that have been described previously.[21,22] In the other three cases active treatment with cortisone was being carried out, and probably in each instance was a factor in death.

The major toxic reactions were similar to those described by others except in two instances. One case developed a leukopenia while receiving intramuscular injections of cortisone but later developed a normal blood picture when taking this drug orally. This was never completely explained but probably was due to one of the inactive vehicles in which the cortisone was dissolved.[17] In the other instance the patient showed an increase of a previously existing exophthalmos and the drug was discontinued. There was never any evidence of hyperthyroidism and the cortisone may have had no influence on the condition.

Minor toxic reactions were for the most part similar to those reported by other observers. Any unusual clinical development in a patient taking cortisone is apt to raise some concern on the part of the physician and alarm on the part of the patient and family. A severe tracheobronchitis in one patient, and the development of retinal vein thrombosis in another, were the cause of considerable apprehension but hardly due to the treatment. Two patients developed annoying sore tongues with negative physical findings. The condition subsided spontaneously within a few months. The two cases of hip fracture resulted from falls and could have occurred in individuals of similar age and circumstances who were not receiving cortisone. No spontaneous fractures were noted.

The long-term management of any disease raises problems of drug tolerance, regularity of administration and the patient's willingness to follow directions. Many cases in this series not being under direct or close supervision, difficult problems arose because of the toxic potentialities of cortisone. In spite of a respect for the drug and directions to the contrary, many patients showed a striking laxness toward or a complete disregard for instructions. The dose was often increased to alarming levels, supplementary potassium was discontinued, the low sodium diet ignored and the urine examinations for sugar dismissed as too troublesome. It was often difficult to have them report regularly for blood pressure determinations, weight comparisons or chest x-rays. To initiate cortisone therapy in rheumatoid arthritis is a major procedure and should never be entered into casually or without realizing that it will have to be continued indefinitely and accompanied by a certain amount of danger. Particularly to be condemned is the careless practice of supplying a patient with enough of the drug to last two or three weeks, and leaving him under the impression that this will affect a cure. This is either wishful thinking, lack of information or a desire to placate a complaining patient.

In spite of its therapeutic limitations and toxic effects, cortisone has a useful place in the treatment of rheumatoid arthritis and should certainly be utilized in active cases progressing to a crippling deformity when other measures have failed. It is often helpful in elderly patients with mildly active disease who can be controlled on a small dose of the drug and in whom comfort is the main objective.

SUMMARY

1. At the end of three years, eleven cases (31.1 per cent) of an original group of thirty-five patients with rheumatoid arthritis treated with cortisone have been benefited sufficiently to continue the drug. None of these patients suffered any serious adverse reaction.

2. Five deaths occurred in the series, four of which were probably directly or indirectly the result of cortisone. In one instance death occurred twenty months after the drug had been discontinued.

3. Adverse or toxic reactions of a nature and severity sufficient to discontinue treatment developed in ten cases. In two of these, however, it was doubtful that the cortisone was entirely responsible.

4. Minor adverse or toxic reactions were encountered often and in a variety of forms. Many

miscellaneous clinical conditions developed in this group during the course of cortisone treatment and were always a source of considerable apprehension and concern on the part of both the physician and the patient. Many of these had no direct or indirect relationship to the treatment, and it was important to evaluate these situations correctly.

5. Cortisone has a definite but limited use in the maintenance management of rheumatoid arthritis. It should not be used routinely but only after other measures have been adequately tried.

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Diagnostic Significance of Pulmonary Hypertrophic Osteoarthropathy*

ALFRED VOGL, M.D., SERGE BLUMENFELD, M.D. *and* LEONARD B. GUTNER, M.D.
New York, New York

CLUBBING of the fingers and toes is a familiar phenomenon first described in the writings of Hippocrates (hence the term "Hippocratic fingers"). Not until many centuries later did Bamberger[2,3] in Vienna (1889) and Marie[29] in Paris (1890) independently recognize it as part of a more widespread disorder with a typical clinical and pathologic picture which Marie named "pulmonary hypertrophic osteoarthropathy." This should not be confused with a hereditary and familial type of clubbing which was later identified as an unsightly but innocuous peculiarity.[48] Clubbing of the fingers and toes, when acquired later in life, is the outward manifestation of a visceral and often serious disorder. Most often it is seen as part of the classical triad of clubbing, periostitis and synovitis associated with chronic chest disease and then referred to as "pulmonary" osteoarthropathy.

The obscure nature of this syndrome and its often bizarre and confusing clinical picture have continued to fascinate clinicians and investigators. The question of its pathogenesis has aroused much speculation but remains as yet unanswered. Recently, the subject has attracted new and heightened interest because of two developments, one diagnostic and one therapeutic:

1. In an increasing number of observations clinical manifestations of osteoarthropathy have preceded any local symptoms of pulmonary carcinoma. The time interval between these two groups of symptoms appears sufficiently long and the incidence of osteoarthropathy in those cases high enough to point to the important role pulmonary osteoarthropathy may play in the early diagnosis of some cases of cancer of the lung.

2. It has been realized that pulmonary osteoarthropathy may not be merely a minor phenomenon incidental to more serious chest disease but that it is often in itself the cause of protracted invalidism and of great suffering, simulating other intractable painful disorders such as progressive rheumatoid arthritis. Moreover, the condition is reversible and promptly cured by elimination of the underlying, usually intrathoracic, pathologic process.

The cases to be reported may serve to emphasize these two points and also to illustrate the classical picture of pulmonary osteoarthropathy since it may be a source of diagnostic confusion. An early correct diagnosis may help to avoid misdirected therapy and suggest a direct attack upon the primary cause of the illness.

CASE REPORTS

CASE 1. J. H., a forty-four year old white man, was admitted because of cough of two months' duration. Shortly after the onset of this cough he began to suffer from severe pain in his fingers, both knees, legs and ankles. The affected parts became red and swollen. The pain was intensified by even mild pressure, such as crossing the legs.

Five years earlier the patient had been hospitalized in an Army hospital for ten months because of a painful condition of his right chest. A diagnosis of "lung cyst" was made at that time.

On admission to Metropolitan Hospital the patient appeared chronically ill. The chest was emphysematous and hyperresonant with decreased breath sounds throughout. The distal phalanges of all fingers were red and bulbous. The legs appeared flushed, were markedly edematous to the knees and were exquisitely tender, especially on pressure on the tibias. X-ray examination showed dense infiltration of the left upper lobe, interpreted as tuberculosis. In

* From the Department of Medicine, Metropolitan Hospital, and the Department of Therapeutics, New York University College of Medicine, New York, N. Y.

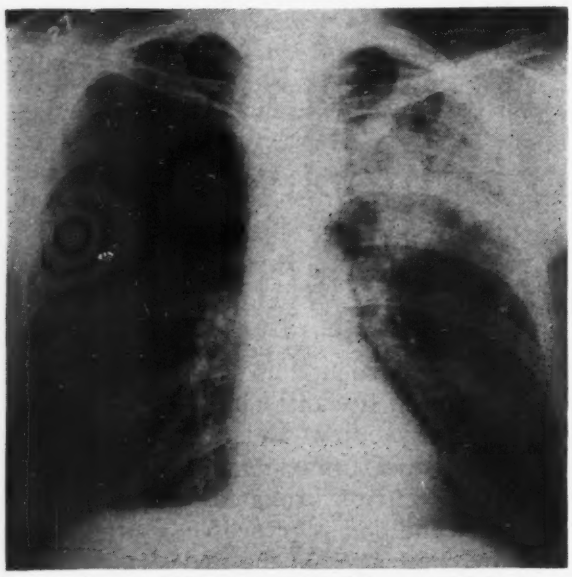


FIG. 1. Case I. A forty-four year old man with infiltration of the left upper lobe, diagnosed as tuberculosis, and huge air cyst occupying the right upper lobe.

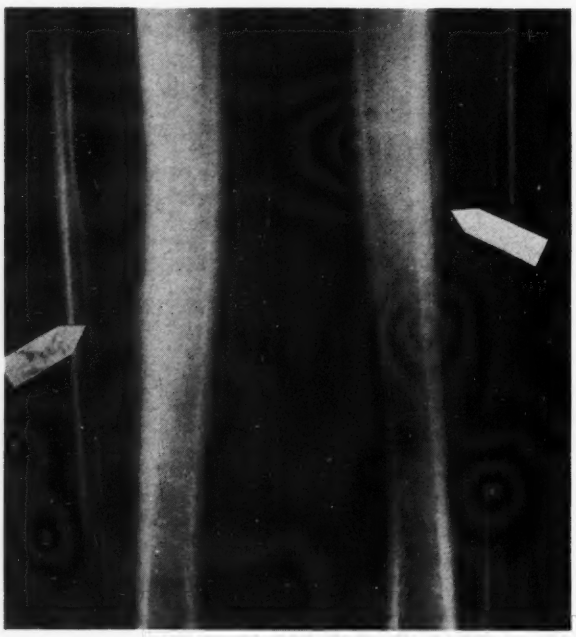


FIG. 2. Case I. Periosteal thickening of both tibias and fibulas as part of pulmonary osteoarthropathy.

the right upper lobe a huge, thin-walled air cyst was seen. (Fig. 1.)

In the hospital the course was increasingly febrile despite the administration of antibiotics. Serial x-rays showed progression of the lesion more toward the hilum than toward the periphery, conspicuously sparing the apex. Several sputa were found negative for tubercle bacilli. For all these reasons tuberculosis was considered unlikely and pulmonary carcinoma suspected even though no tumor could be demonstrated by bronchoscopy.

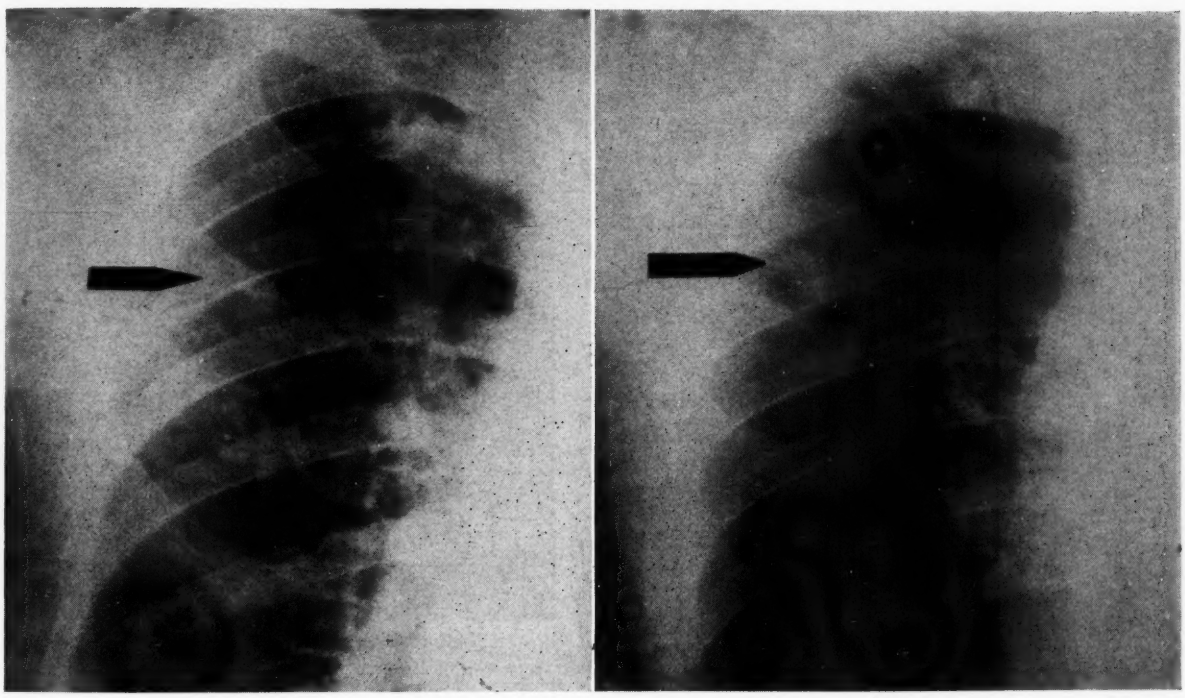
Initially the painful condition of the extremities was interpreted as an acute polyarthritis of unknown origin. The diffuse swelling and reddening of the legs was ascribed to a complicating thrombophlebitis. However, x-ray examination showed extensive, proliferative periostitis of the femurs, tibias and fibulas. (Fig. 2.) These x-ray findings, supplementing the clinical picture, established the diagnosis of pulmonary osteoarthropathy.

An exploratory thoracotomy, later performed at another institution, revealed an inoperable adenocarcinoma of the left lung.

Summary: In this patient with advanced pulmonary carcinoma the symptoms and signs of severe pulmonary osteoarthropathy appeared concomitantly with the chest symptoms. They were, however, more prominent than the complaints referable to carcinoma of the lung, and the patient's chief complaint on admission.

CASE II. J. B., a fifty-six year old white man, had been well until about four months before his first examination, except for a long-standing "cigarette cough." At that time he noticed pretibial and ankle edema which would increase toward evening. Congestive heart failure, flat feet and deep varicose veins were alternately considered as diagnostic possibilities. A chest film taken at that time was regarded as negative. (Fig. 3A.) During the following months he began to suffer from stiffness of the knuckles and knees, severe burning pain ("like a furnace") in the soles and lower part of both legs, and soreness over the tibial crests. Lowering of the legs aggravated the pain and finally made such a position almost intolerable. During the last week his temperature rose to 101°F. and night sweats appeared.

Physical examination of the chest revealed a few scattered post-tussic rales. The legs below the knees were markedly edematous; the skin was red, shiny and very warm. The shins were intensely tender to light pressure. The toes showed mushroom-like clubbing and purple discoloration. The fingertips were also clubbed. The sedimentation rate was high. Chest films and tomograms showed a small well defined shadow in the right upper lobe, connected with the hilum by a broad dense strand. (Fig. 3B.) X-rays of the legs revealed slight but definite irregular periosteal thickening of both tibias and



3A 3B

FIG. 3. Case II. A, chest film of a fifty-six year old man at the time of the onset of leg pain and swelling; interpreted as negative. Note the delicate shadow at the level of the second right anterior intercostal space. B, four months later the round shadow, hardly noticeable on the original film, has become more definite.

fibulas. (Fig. 4A.) In view of the presence of pulmonary osteoarthropathy the pulmonary mass was interpreted as most likely malignant. On lobectomy a squamous cell carcinoma of the right upper lobe was found.

The pain in the legs as well as the edema disappeared on the first day after the operation and did not reappear even when the patient dangled his legs the following day. The sensation of stiffness of the knuckles and knees was gone by the third postoperative day. Clubbing and redness of the toes decreased gradually and the skin of the legs became dry and wrinkled, resembling the picture of ichthyosis.

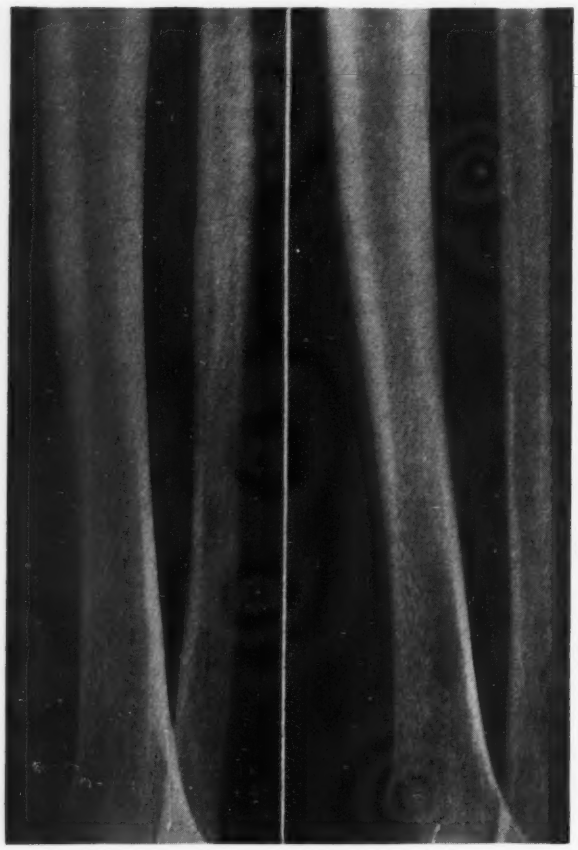
Three months later x-rays of the extremities showed subsidence of the periosteal thickening and reappearance of smooth bony outlines. (Fig. 4B.) The sedimentation rate returned to normal.

About six months later the patient developed severe pain in the back and right shoulder, and increasing dyspnea and stridor with evidence of metastatic involvement of the mediastinal and tracheobronchial lymph nodes. Despite this obvious intrathoracic spread of the neoplasm neither symptoms nor signs of pulmonary osteoarthropathy recurred.

Summary: Symptoms of pulmonary osteoarthropathy preceded by more than four months the detection of a small asymptomatic intrapulmonary lesion by x-rays. Bronchogenic carcinoma was suspected chiefly because of the presence of osteoarthropathy. Immediate and complete relief from the distressing osteoarticular condition followed lobectomy; it did not recur when mediastinal lymph node metastases developed six months later.

CASE III. J. K.,* a fifty-eight year old house painter, complained of intermittent and gradually increasing dysphagia and vomiting of approximately twenty-five years' duration. During these episodes he had difficulty in swallowing all foods, liquid as well as solid. There was no pain and no weight loss. In 1947 he suffered a fracture of his left hip. Between 1948 and 1951 he had noticed progressive enlargement of the tips of his fingers and toes. In July, 1951, he was found pale and emaciated, with marked clubbing of all digits. A chest x-ray revealed no intrapulmonary lesions, but there was marked widening of the mediastinal shadow with a

* This patient was seen in consultation with Dr. Louis L. Perkel and Dr. Leonard Troast of Jersey City who kindly permitted the use of this case for publication.



4A 4B

FIG. 4. Case II. A, periosteal proliferation is demonstrable as a thin irregular shadow at the medial border of the fibula. B, three months after lobectomy the outlines of the bones have resumed a perfectly smooth appearance.

fluid level in the upper third. A barium swallow demonstrated this to be an enormously dilated and tortuous esophagus with cardiospasm.

Two months later cardioplasty was performed. The patient was seen again three months after the operation. The dysphagia had improved but in the preceding month he had developed fever ranging to 103°F., severe normocytic anemia and marked edema of the legs (for which he had received mercurial diuretic injections elsewhere). On x-ray examination some emptying of barium into the stomach was demonstrable even though the caliber of the esophagus had not changed. Except for evidence of a recently developed bronchopneumonia the chest films showed no lesion in the portions of the lungs not obscured by the dilated esophagus. (Fig. 5.)

A few weeks later severe pain over the lateral aspect of the left hip, increasing edema of the ankles and stiffness of the fingers appeared. X-rays of the extremities showed marked

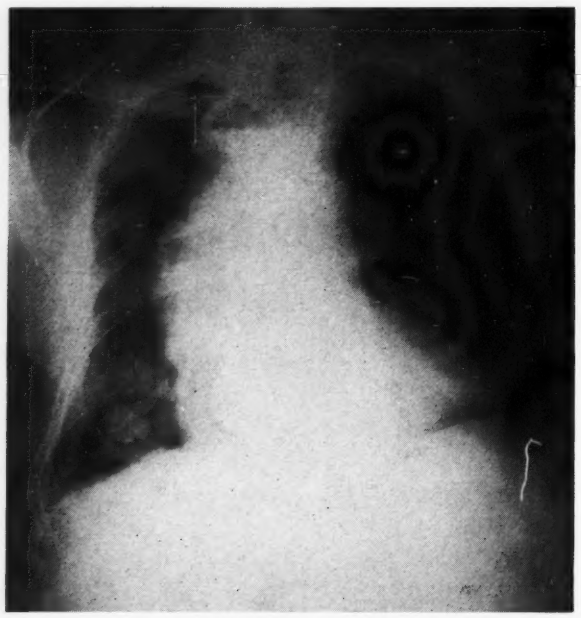


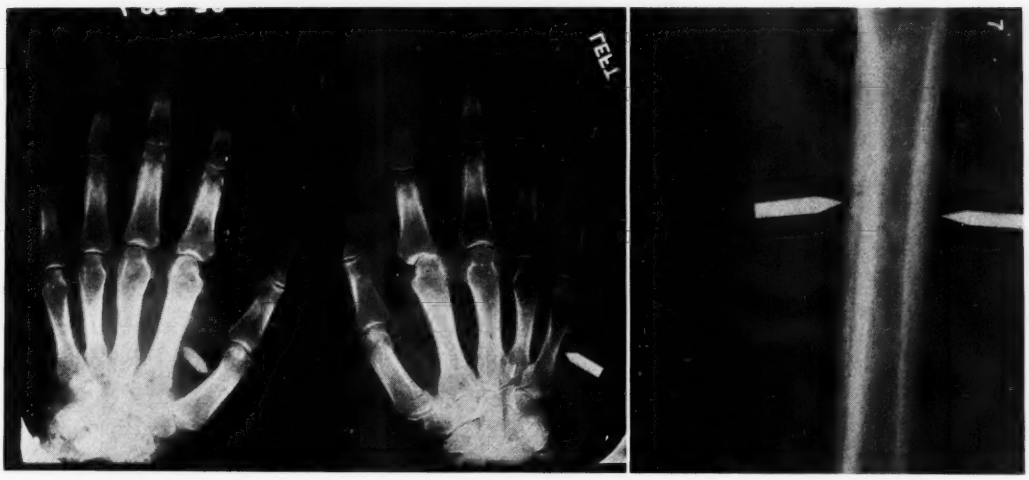
FIG. 5. Case III. A fifty-eight year old man with cardiospasm of about twenty-five years' standing and enormously dilated esophagus. Note fluid level above the first rib. At the right base there is patchy cloudiness (bronchopneumonia).

periosteal proliferation of all the metacarpals, metatarsals and proximal phalanges (Fig. 6) and enormous lamellar thickening of the periosteum of the shafts of the humerus and femur on both sides. (Fig. 7.) In addition there was a small area of destruction at the lateral aspect of the left greater trochanter.

The patient's condition deteriorated rapidly, with persistent high fever, marked dyspnea, weakness and appearance of a right pleural exudate. He died a month later. Biopsy of the left hip revealed metastatic squamous cell carcinoma, source unknown. Autopsy was refused.

Summary: In this case it is conceivable that the symptoms of pulmonary osteoarthropathy (including clubbing for three years and an extraordinary degree of periosteal proliferation) were secondary to the presence of an extremely dilated esophagus which may have acted for many years like a benign mediastinal tumor. However, in view of the biopsy revealing a metastatic squamous cell carcinoma in the femur the co-existence of a pulmonary carcinoma cannot be ruled out.

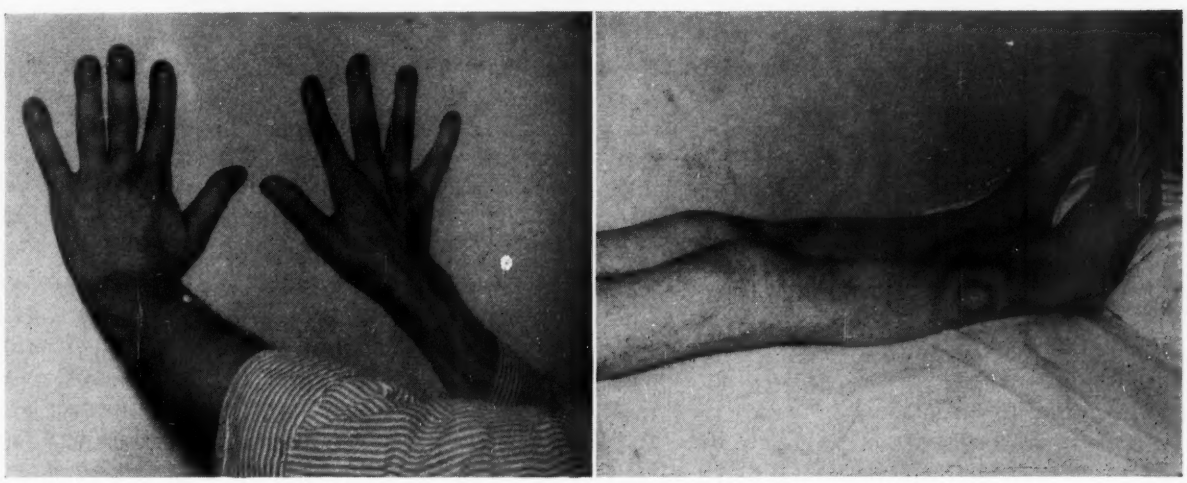
CASE IV. H. S., a forty-five year old white man, a chronic alcoholic, sought admission to Metropolitan Hospital because of pain and swelling of both legs of four weeks' duration.



6 7

FIG. 6. Case III. Marked periosteal thickening of all metacarpals and the basal phalanges.

FIG. 7. Case III. Enormous lamellar periosteal thickening of the femur.



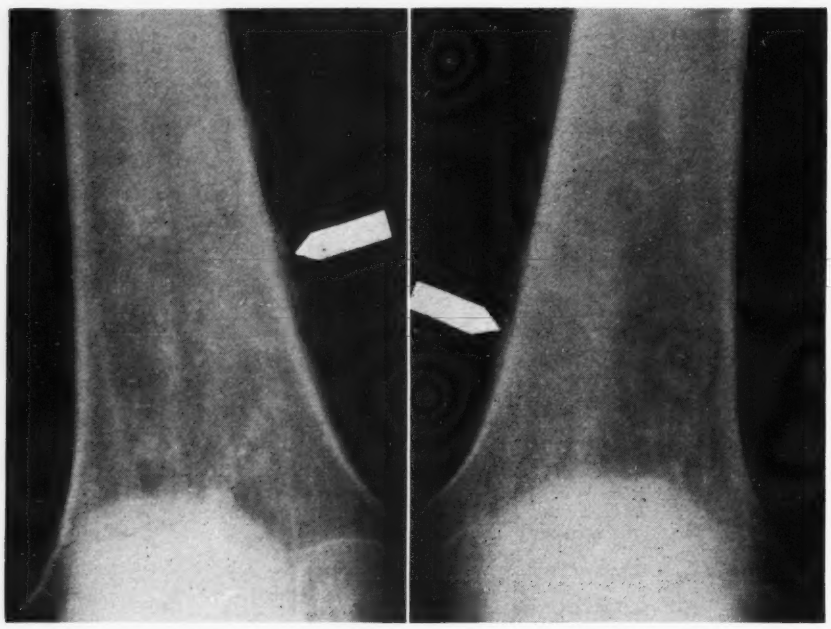
8A 8B

FIG. 8. Case IV. A, clubbing and redness of finger tips on admission for pain and swelling of legs and productive cough in a forty-five year old man. B, the legs are swollen, reddened, warm and extremely tender; the toes are clubbed.

Originally, these symptoms disappeared on elevation of the legs but gradually they became more severe and persistent. The leg pain was described as diffuse, deep-seated and worse at night. The swelling was marked and involved the feet, ankles and the distal two-thirds of both legs. During the preceding few months the patient had lost 10 to 15 pounds and had become progressively weaker. A month prior to admission he became unable to work and developed right chest pain and a cough productive of large amounts of greenish, frequently blood-streaked sputum.

There were diminished breath sounds in both lungs but no rales. Marked clubbing and redness of the tips of fingers and toes were present. The feet, ankles and pretibial regions were reddened, markedly edematous (Figs. 8A and B) and exquisitely tender to pressure and the skin temperature over these areas was noticeably elevated. Passive motion of the ankle joints was very painful. Pulmonary tuberculosis was suspected on admission, and the findings in the extremities were ascribed by various observers to cirrhosis, rheumatoid arthritis, nutritional edema, or beriberi heart disease, but finally the diagnosis of pulmonary osteoarthropathy was agreed upon on clinical grounds.

Chest x-rays showed a cavity at the level of the right clavicle. X-rays of the lower extremities



9A 9B

FIG. 9. Case IV. A and B, patchy, coarse, periosteal thickening of the distal third of the femora.

showed marked patchy periosteal thickening of the distal third of the femurs and proximal third of the tibias. (Fig. 9.)

Repeated sputum examinations were negative for tubercle bacilli. Bronchoscopy revealed thick greenish sputum emanating from the right upper lobe bronchus. A diagnosis was made of chronic lung abscess, probably following aspiration pneumonia.

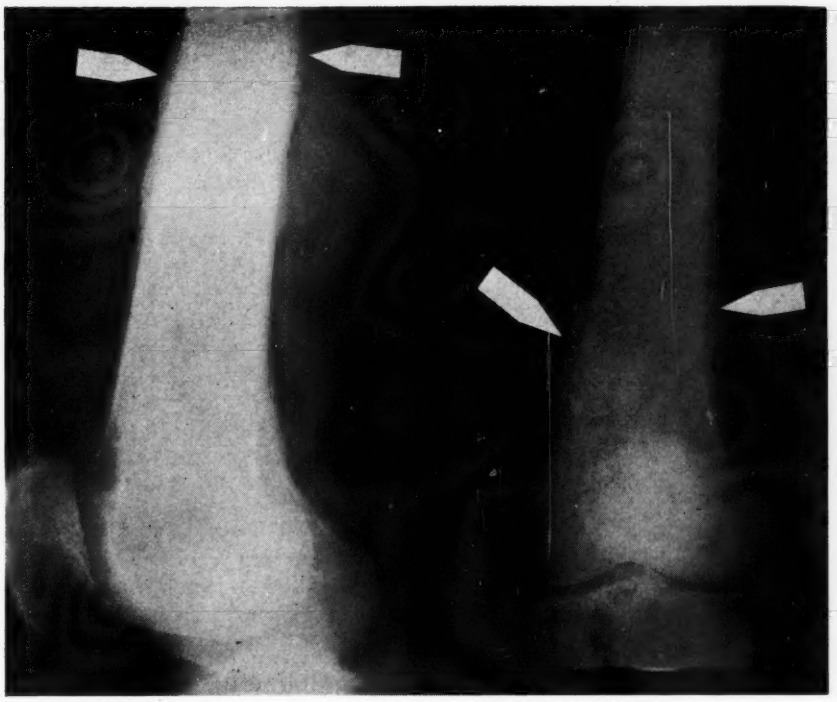
Treatment consisted of terramycin® and postural drainage. The sputum decreased considerably and rapidly in quantity and the size of the cavity appeared somewhat reduced after five weeks of hospitalization. Simultaneously, pain and redness of the legs subsided almost completely.

Summary: In this case the symptoms of pulmonary osteoarthropathy were accounted for by a chronic lung abscess. They had appeared at about the same time as the cough. Successful conservative treatment of the pulmonary infection was followed by marked subjective and objective subsidence of all the symptoms of osteoarthropathy.

CASE V. C. F.,* a forty-five year old white male executive, was first seen in November, 1952, when he complained of malaise, weakness, chilliness, sweating and generalized aches of several weeks' duration. Physical examination revealed no abnormalities but the urinalysis showed 10 to 12 red cells per high power field and the sedimentation rate was very rapid. Approximately four weeks later the patient began to note afternoon temperatures up to 101°F., pain, warmth, swelling and limited motion of the ankles, knees and wrists, with stiffness of these same joints in the morning and on inactivity. The edema of the ankles and legs would increase toward the end of the day. There had been a weight loss of 6 pounds during this interval.

Marked improvement followed the administration of cortisone orally and weekly gold injections were instituted, based upon a presumptive diagnosis of acute rheumatoid arthritis. Cortisone was stopped because of the development of severe epigastric gnawing pain and heartburn but the gold injections were continued until May 1, 1953, without much improvement. Clubbing of the fingers and toes developed rather suddenly about the third week in April and progressed rapidly. X-rays of the knees showed no abnormality of the joint surfaces but the adjacent portions of the distal femora revealed lamellate periosteal proliferation. (Figs. 10 and 11.) A chest film taken at the same time revealed an 8 by 10 cm. lobulated soft tissue mass in the apical and subapical

* We wish to thank Drs. James Flexner and John Wolf of White Plains for allowing us to include this case.



10 11

FIGS. 10 and 11. Case v. A forty-five year old man with an asymptomatic large tumor mass in the left lower lobe and symptoms suggestive of rheumatoid arthritis. Joints appear normal but periosteum of distal thirds of femora shows marked lamellate thickening.

portions of the left lower lobe. At no time during the course of this patient's disease were there any complaints or physical findings referable to the respiratory system.

On June 3, 1953, a left pneumonectomy was performed and several hilar and mediastinal lymph nodes were removed. The pathologic diagnosis was that of a large adenocarcinoma arising from a branch bronchus of the left lower lobe with spread to the regional nodes.

The joint discomfort and limitation of motion vanished shortly after the patient awakened from the anesthesia. The swelling of the ankles, legs and knees receded strikingly during the first postoperative day and had essentially disappeared by the second. On re-examination five months later no trace of joint or bone involvement was found and the previously pronounced clubbing had almost vanished. The absence of any recurrence of these phenomena is the more noteworthy since several round shadows, obviously metastases, were found in the right lung at this time. (Fig. 12.)

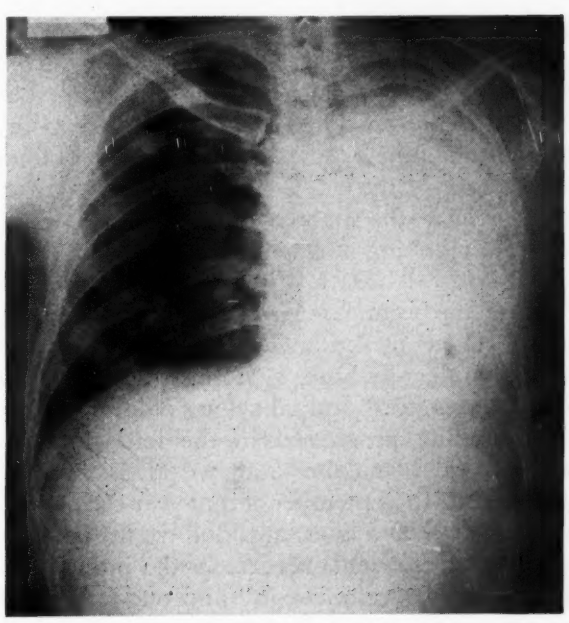


FIG. 12. Case v. Six months after left pneumonectomy there is no recurrence of symptoms of osteoarthropathy despite metastatic involvement of the remaining lung.

Summary: This patient presented symptoms and physical abnormalities highly suggestive of an acute form of rheumatoid arthritis from the onset of his illness. It was not until six months later when, in the absence of any respiratory symptoms, the appearance of typical clubbing directed attention to the lung and the diagnosis of bronchogenic carcinoma associated with

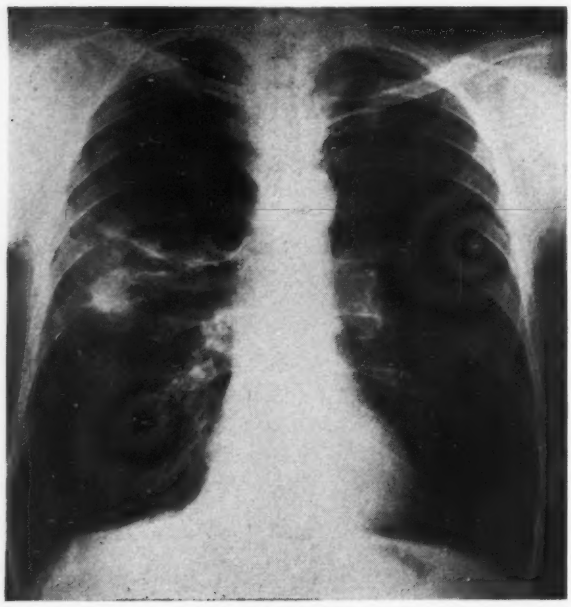


FIG. 13. Case VI. Case of bronchogenic carcinoma masquerading as infected lung cyst in a fifty-three year old man. Large, thin-walled air cyst in the right upper lobe, apparently under tension; also a round shadow and atelectatic plates in the right middle lung field are seen (September, 1953).

hypertrophic osteoarthropathy was established. Here, as in Case II, pneumonectomy produced immediate complete remission of the osteoarticular manifestations. They had not recurred when, six months after the operation, numerous metastases were evident radiographically in the remaining lung. This case also exemplifies occurrence of the other symptoms and signs of osteoarthropathy six months before the development of clubbing of the digits.

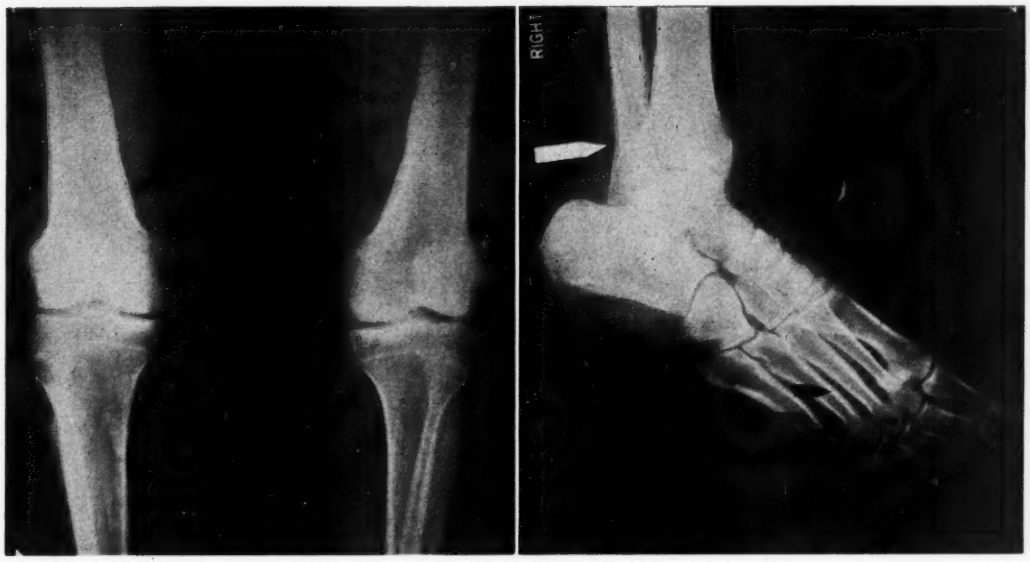
CASE VI. A. D., a fifty-three year old white electrician, began to complain of pain, stiffness and swelling of the ankles, legs, knees, elbows and shoulders in June, 1953. Despite treatment with butazolidin® and salicylates pain, disability and swelling progressed in the following few months, and malaise and weakness became prominent. In September of that year the patient complained of a constant dull right anterior chest ache, a recent increase in the intensity of his usual "cigarette cough" and one episode of minimal hemoptysis. He had noted the development of clubbing in the preceding five weeks. At that time clubbing of all fingertips, some swelling and tenderness of the proximal interphalangeal joint of the left index finger, and slight swelling and tenderness over the tip of the right olecranon process were present as well as warmth, moderate periarticular swelling and tenderness of the ankles and knees. Pitting edema was present over both tibias to just below the level of the knee. The hands and feet were moderately cyanotic. Examination of the chest revealed diminution of breath sounds below the right scapula and the presence of scattered rhonchi. The white blood count was 25,600 with 78 per cent polymorphonuclears and the hemoglobin was 10.5 gm.

A chest film demonstrated bilateral multiple emphysematous blebs and a fluid level in a large air cyst in the apex of the right lower lobe. (Fig. 13.) X-rays of the tibias, fibulas, femurs, radiuses, ulnas and hands exhibited findings typical of hypertrophic osteoarthropathy. (Figs. 14 and 15.)

The patient was treated with a course of penicillin for two weeks. The chest pain disappeared in two days; the joints were much less painful and warm and the swelling was almost gone in another few days. At the end of the first course of antibiotic therapy the joints were no longer painful, swollen or warm, though some periarticular thickening remained, and the clubbing had receded considerably. Cough and sputum cleared completely and the white blood count dropped to 12,900. The residual joint stiffness responded to oral cortisone therapy and serial x-ray studies revealed disappearance of the fluid level and considerable decrease in the size of the cavity.

Two months later pain recurred in the left anterior chest and the white count rose to 28,000. Chest films revealed the reappearance of a fluid level apparently in the same cavity which, however, appeared much smaller at this time. Despite the obvious presence of infection, there were, at first, only mild symptoms and signs of osteoarthropathy. They increased, however, gradually and finally became severe, with uncontrollable bone and joint pain accompanied by elevated temperatures, sweats and progressive weight loss. Reinstitution of intensive antibiotic therapy proved ineffective this time. Finally, exploration of the chest was performed in February, 1954, and revealed bronchogenic carcinoma, obviously too far advanced for radical removal. Palliative pneumonectomy was performed. Joint and bone pain and swelling disappeared completely in the immediate postoperative period.

Summary: This is a case of cystic lung disease, probably secondary to bronchogenic carcinoma, which was complicated by infection and possible



14 15

FIG. 14. Case VI. Marked periosteal proliferation of femora, tibias and fibulas.

FIG. 15. Case VI. Periosteal thickening of tibia, fibula and metatarsals.

ballooning of an air cyst, and associated with an acute form of hypertrophic osteoarthropathy. Symptoms of multiple periostitis and synovitis preceded the development of clubbing by two and a half months, and the appearance of the first definite respiratory symptoms by four months. They initially receded markedly when antibiotic therapy was instituted. The fluid level disappeared and the air cyst, which apparently was under tension, collapsed.

Two months later there was recurrence of increasingly severe symptoms of osteoarthropathy together with the reappearance of signs of pulmonary infection. The general downhill course and the intractability of the pulmonary infection and of the osteoarticular manifestations led to surgical exploration and detection of an underlying pulmonary carcinoma. While intensive antibiotic therapy initially induced transient remissions of the osteoarthropathy, palliative resection of the carcinomatous lung was followed by an immediate and complete cessation of all the symptoms in the extremities. This case also indicates that persistence of active osteoarthropathy in a treated case of chronic lung abscess should arouse suspicion of an underlying malignant process.

CASE VII. H. S., a fifty-five year old white man, was admitted to Metropolitan Hospital because of cough and pain in the left chest of about ten weeks' duration, and progressive weight loss despite good appetite. The cough produced yellowish sputum. The chest pain was constant and aggravated by deep inspiration.

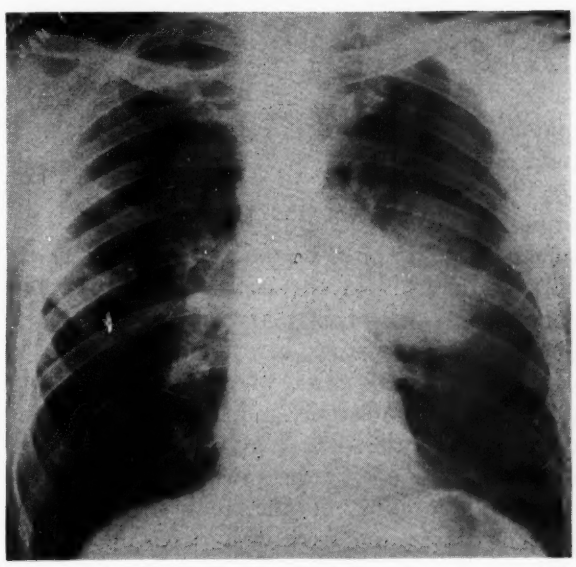
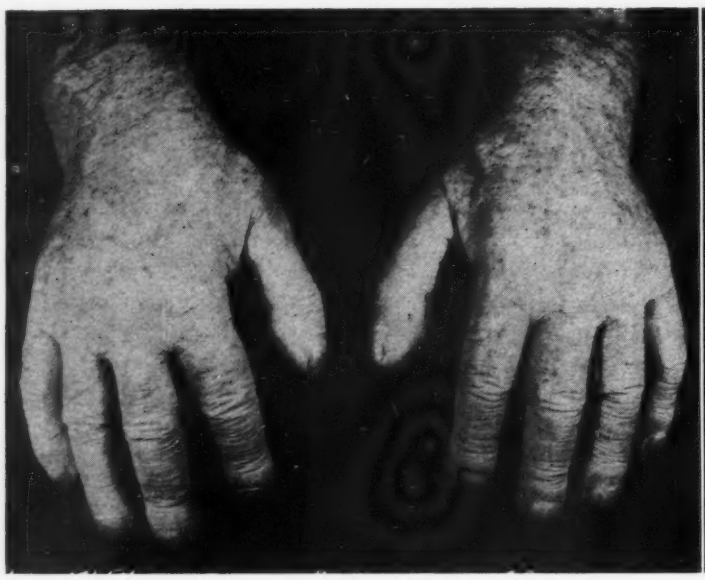


FIG. 16. Case VII. Cough and chest pain of ten weeks' duration in a fifty-five year old man. Chest film shows large perihilar shadow apparently involving the cranial portion of the left lower lobe.

On admission dullness was found in the left interscapular region and diminution of breath sounds over the left upper lobe. Temperatures ranged between 100° and 101°F. X-ray examination of the chest (Fig. 16) revealed a large dense shadow in the left middle lung field, apparently involving the apical segment of the lower lobe.

In the course of the first four weeks of hospitalization, the patient began to complain of stiffness



17

18

FIG. 17. Case VII. During the first month in the hospital, stiffness and pain in the wrists and fingers appeared accompanied by a rapid development of clubbing and swelling of the forearms.

FIG. 18. Case VII. During the first month of hospitalization severe pain in ankles, knees and thighs and marked swelling of the ankles developed. The affected parts were red, warm and exquisitely tender; the toes became clubbed.

and aches in his wrists and fingers and severe pain in his ankles which gradually spread up to the knees and thighs and made walking virtually impossible. At the same time clubbing of the fingers and swelling of the forearms (Fig. 17) and particularly of the ankles appeared. The edema increased rapidly and soon involved legs and feet. Congestive heart failure was first considered as the cause of the edema but the presence of continuous pain, the pronounced tenderness of the iliac crests, the redness and warmth of the edematous parts and the appearance of clubbing of the toes suggested an acutely developing form of hypertrophic osteoarthropathy. (Fig. 18.) This assumption was corroborated by the radiologic demonstration of patchy periosteal thickening of the distal portions of the radiuses and ulnas and of some metacarpals, and of extensive symmetrical periosteal ossification of both tibias (Fig. 19) and all the metatarsal bones. (Fig. 20.)

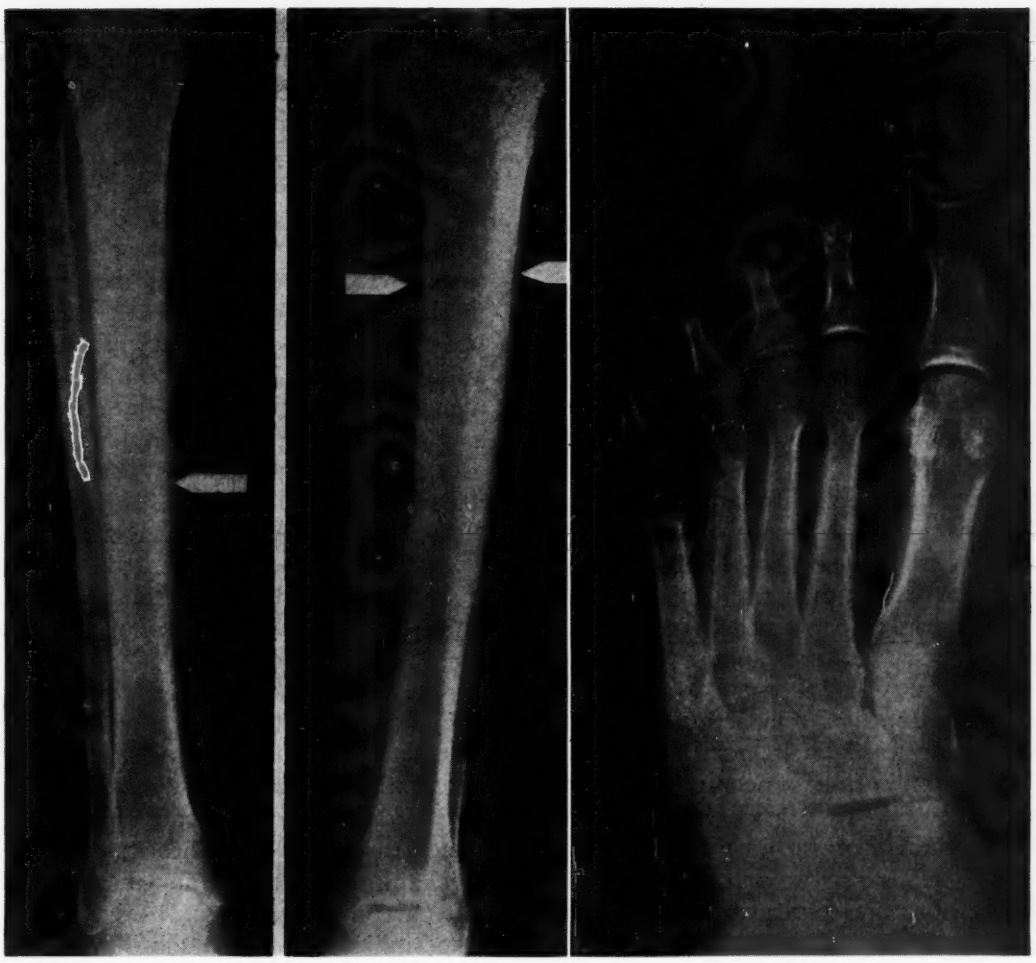
Bronchoscopy supplied no conclusive result. Exploratory thoracotomy was performed and an apparently operable tumor of the left lung with involvement of the mediastinal nodes was found. Pneumonectomy was performed. The tumor was found to be a squamous cell carcinoma with metastases to the regional lymph nodes.

The pain in the extremities as well as the tenderness of the bones disappeared within three days following the operation. The edema of the legs, however, subsided more slowly. Two months after the operation the edema of the legs was completely gone, the tibias were non-tender and the skin very dry, wrinkled and of tree-bark appearance.

Summary: In this case the symptoms of osteoarthropathy became apparent only about two months after the onset of the chest symptoms. The extent of periosteal bone formation visible at that time makes it likely, however, that these periosteal changes had been present a considerable time before clubbing and pain appeared, and could have been demonstrated by x-rays. In this patient, in whom the clinical and radiologic chest findings did not permit a definite preoperative differentiation between inflammatory and neoplastic disease, radiologic demonstration of hypertrophic osteoarthropathy favored the diagnosis of malignant lung disease.

COMMENTS

These case reports illustrate the classical features of pulmonary hypertrophic osteoarthropathy: (1) Bone pain, which frequently is acute in onset, deep-seated, burning in character and aggravated by lowering of the extremities; (2) stiffness of the fingers; (3) muscular weak-



19 20

FIG. 19. Case VII. Extensive irregular periosteal thickening of the tibias and fibulas.

FIG. 20. Case VII. Severe periosteal proliferation of the metatarsal bones and proximal phalanges.

ness; (4) broadened or cylindrical appearance of the distal thirds of the extremities produced by a firm, hardly pitting edema; (5) redness, glistening, warmth and perspiration of the skin of the affected regions; (6) intense tenderness to pressure over the affected bones and pain on passive motion of the adjacent joints; (7) progressive clubbing and dusky discoloration of the tips of fingers and toes; (8) rapid disappearance of pain and swelling after successful treatment of the underlying process.

It is noteworthy that in five of our seven cases the symptoms referable to the extremities represented the chief complaints on admission.

The radiologic picture in our cases was typical: fairly symmetrical, coarse or lamellar subperiosteal bone formation along the diaphyses of the long bones, including metatarsals, metacarpals and proximal phalanges. The newly formed periosteal bone is usually thickest near the distal epiphyses of the long bones and particularly at the lines of musculotendinous insertions.[13]

Our cases also serve to emphasize points which have been the subject of some discussion in the literature:

1. There is a wide variety of associated chest lesions, which may range from chronic suppuration (lung abscess, infected lung cysts, bronchiectasis, pleural empyema, blastomycosis[11]) to intrathoracic neoplasms of all types, malignant (pulmonary carcinoma, thymoma,[33] fibrosarcoma,[5,51] lymphoma,[50] endobronchial plasmocytoma[37]) or benign (fibroma,[15,41,51] hemangioma, pleural mesothelioma,[38] lipoma, dermoid,[33] neurofibroma,[25] bronchogenic cyst [34,50]), possibly even "pseudotumors" such as a grossly dilated esophagus (Case III). Only rarely have hematogenous metastases to the lungs been recorded as associated with either

the soft-part or the periosteal changes of pulmonary osteoarthropathy (metastatic fibrosarcoma,[42] metastatic giant cell tumor[30]). The presence of osteoarthropathy therefore heavily favors the diagnosis of a primary pulmonary neoplasm over that of a metastasis. Neither in our Case III nor in Case V did the symptoms of osteoarthropathy which disappeared after operation recur when extension to the tracheobronchial lymph node or multiple metastases to the remaining lung, respectively, developed about six months later. In case of local recurrence, however, such as happened in three patients operated upon for pleural mesothelioma, regrowth of the tumor was accompanied by reactivation of the osteoarthropathy.[38]

2. There is a high incidence of hypertrophic osteoarthropathy in cases of malignant lung tumors, irrespective of their size. This complication was found in 10 per cent of a series of 139 cases of pulmonary carcinoma, more particularly of the peripheral type.[42]

3. The symptoms of osteoarthropathy may precede by one to eighteen months[6] any pulmonary symptom in cases of neoplastic disease of the chest[1,4,6,12,17,18,23,36,39,44,50,51] in contrast to suppurative chest processes in which the onset of symptoms of osteoarthropathy tends to lag behind unmistakable respiratory and systemic manifestations.

4. There may be considerable difficulty in recognizing the true nature of the condition and in differentiating it from other diseases as diverse as rheumatic, rheumatoid or infective arthritis,[18,30,44,50] thrombophlebitis, congestive heart failure, venous stasis, nutritional edema, peripheral neuropathy or acromegaly.

5. Pain and swelling may vanish rapidly after elimination of the primary disease[4,5,15,18,22,25,35,36,50,51] so that one patient, e.g., after five years of severe suffering, became comfortable within twelve hours of removal of an intrathoracic fibroma.[16] The distressing symptoms of osteoarthropathy disappeared within a day of pneumonectomy for pulmonary carcinoma in several cases, even though involvement of the regional lymph nodes was present at that time (our Cases II, V, VI and VII), an experience which should encourage *palliative* lobectomy in cases of uncontrollable skeletal pain (Case VI).

Experiences such as the prompt improvement following excision of non-malignant and non-suppurative chest lesions must obviously influence any consideration of the pathogenesis of pulmonary osteoarthropathy. It seems to the authors that pathologic processes capable of such rapid regression are most likely to be in the nature of a reversible local circulatory disorder causing hyperemia and edema. Edema within the connective tissue of the pulp has been demonstrated in an amputated clubbed finger.[8] The presence of increased vascularity in clubbed fingers was first suggested by the capillaroscopic finding of enormously dilated vessels in the nail beds[43,46,47] (and confirmed by later studies[22]) and has recently been corroborated by measurements of skin temperature and color[31,32] as well as by infrared photography and postmortem arteriography.[10] The latter revealed a dense network of abnormally wide arteries and arterioles, especially around the ungual processes. The existence of increased local blood flow is further suggested by the observation that the bulbous fingertips tend to collapse promptly and shrivel when the hands are kept elevated, and re-expand when lowered,[10] and that the pain increases markedly after lowering of the legs from the horizontal position (personal observations). Even though these facts offer no clue as to the basic causation of pulmonary osteoarthropathy they throw some light on the mechanism responsible for the changes in the soft parts and periosteum. A sustained increase in peripheral arterial blood flow with capillary stasis could produce the essential pathologic manifestations of osteoarthropathy: the edema and hyperplasia of the finger pulp (clubbing), the synovial exudation (arthropathy) and the periosteal proliferation (osteophythosis[9]).* Conversely, the rapid postoperative improvement may be accounted for by a sudden readjustment of the peripheral blood flow (and the resultant elimination of capillary stasis, edema and excessive tissue tension), possibly through abolition of some obscure pulmonary-vascular reflex mechanism. The validity of this concept could readily be checked by preoperative and immediately postoperative nail bed capillaroscopy and infrared photography. Such studies may greatly contribute to the clarification of the problem of pulmonary osteoarthropathy.

Regression of the bony changes does occur[5] (and can be demonstrated radiologically,[5,40] as in our Case II) in cases in which the chest disease is cured unless the local changes are

* Unilateral clubbing of the fingers has been observed in aneurysm of the aorta or the homolateral subclavian artery.

too advanced and the amount of ossification too great for complete reabsorption. In long-standing cases, therefore, enlargement of the circumference of the affected parts may remain permanent.[40]

On reviewing the more recent literature on pulmonary osteoarthropathy, contradictory statements have been found on some aspects of the subject which invite further discussion:

1. There is no doubt that in most cases clubbing of the fingers can be regarded as an early or a mild manifestation of pulmonary osteoarthropathy, since it usually precedes or accompanies the full development of this condition.[4,14,26,27,31,36] However, in the individual case the diagnosis of pulmonary osteoarthropathy need not necessarily rest upon the demonstration of clubbing of the digits, since this has occasionally been absent in an otherwise typical case[36] (Case II) or may manifest itself later than the bony changes[1,49] (our Cases V and VII).

2. There are no records available of patients in whom periosteal or synovial changes developed after stationary, asymptomatic clubbing had been present for years. In fact, such an occurrence is unknown in uncomplicated congenital cyanotic heart disease[27,40] as well as in cases of familial "drumstick fingers." In other words, *permanent* clubbing of the digits can exist as a distinct pathologic and clinical entity apart from the osteoarticular ("pulmonary") type and without any tendency to develop into it.

3. It is noteworthy that radiologically demonstrable periosteal proliferation of the long bones in patients with malignant chest disease may be asymptomatic, as in case 8 described by Pattison et al.[36] and in our Case VII. Since X-ray examination of the long bones is often omitted in routine examination of chronic chest disorders, the incidence of such an occurrence cannot be estimated at present. In cases of lung disease of undetermined nature the demonstration of periosteal proliferation by x-ray may, however, be of diagnostic value, since the presence of such changes would favor the diagnosis of a neoplastic or suppurative process over that of pulmonary tuberculosis.[24,40,50] We have been unable to find in the recent literature a verified, uncomplicated case of pulmonary tuberculosis associated with hypertrophic osteoarthropathy.

4. So-called *idiopathic* hypertrophic osteoarthropathy (also known as idiopathic familial generalized osteophytosis)[19] should be separated clinically from the "pulmonary" type despite their anatomic and radiologic similarity. Patients with this rare condition resemble to some extent those with pulmonary osteoarthropathy since they share clubbing of the fingers, widespread periosteal thickening of the long bones, metacarpals, metatarsals and basal phalanges, limitation of joint motion and ankle edema.[7] Beyond these common features, however, the picture is entirely different: a striking familial and hereditary incidence, often a leprosy-like thickening of the skin, no associated chest (or other visceral) disease, little or no pain except for the discomfort of restricted joint motion, and a self-limited course extending over several decades.

It is evident from this description that the "idiopathic" type of osteoarthropathy has as little in common with the "pulmonary" type, pathogenetically and clinically, as the congenital form of clubbing has with the type associated with pulmonary disease. It is conceivable that the two conditions of hereditary-familial character, congenital clubbing and idiopathic hypertrophic osteoarthropathy, are related. In any event, the clinical course, as well as the presence of an underlying intrathoracic process, justifies separation of the pulmonary type of hypertrophic osteoarthropathy as a well defined clinical-pathologic entity.

SUMMARY

Seven cases of pulmonary hypertrophic osteoarthropathy are presented.

The difficulty in differentiating this condition from rheumatoid arthritis and various other diseases of the skeletal and nervous system, and from disturbances of the general or peripheral circulation is discussed. Correct diagnosis is important for two reasons: (1) The condition is often very distressing and yields to no treatment other than elimination of the underlying primary disease; (2) it not only indicates the presence of serious disease of the lungs, particularly pulmonary carcinoma, but may precede the appearance of respiratory symptoms in pulmonary carcinoma by several months, and thus aid in its early diagnosis.

Evidence is presented to support the view that abnormally increased peripheral blood flow plays a role in the pathogenesis of pulmonary osteoarthropathy. This derangement of peripheral circulation may be dependent upon some pathologic intrathoracic reflex which is promptly

abolished by surgical removal of the affected lobe or of an extrapulmonary mass.

Despite the identity of the anatomic changes in the hereditary types of congenital clubbed fingers and idiopathic hypertrophic osteoarthropathy with those of the "pulmonary" type of osteoarthropathy, the latter apparently is a separate morbid entity.

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Immunologic Aspects of Penicillin Reactions*

SIGMUND S. WINTON, M.D. *and* ERNEST D. NORA, M.D.
Chicago, Illinois

REPORTS on accidents due to hypersensitivity induced by parenterally administered penicillin have been appearing in the medical literature with increasing frequency. Considering the present day indiscriminate use of this antibiotic for febrile diseases which superficially appear to be of infectious origin, these warnings are timely. Often the etiologic basis of the fever is not determined and on occasion illness caused by lymphoblastomas, malignant lesions, blood dyscrasias, infectious mononucleosis and hypermetabolic diseases has been treated with this antibiotic until the true nature of the disease was recognized. The greatest abuse of penicillin therapy probably has been in the treatment of respiratory infections of viral origin.

Allergic manifestations have been reported varying from innocuous dermatoses to anaphylactic shock and death. It would appear quite possible that additional deaths due to unrecognized penicillin anaphylaxis may have been attributed to sudden coronary occlusion in instances in which an autopsy was not performed. The first fatal case caused by penicillin hypersensitivity was reported by Walbott[1] in 1949. In the subsequent three years, Curphey[2] presented two cases, Thomsen[3] a fourth, Higgins et al.[4] a fifth, Siegal et al.[5] a sixth and Mayer et al.[6] a seventh case. Recently, Feinberg and associates[7] recorded five additional cases with autopsy reports. Many non-fatal anaphylactic reactions due to penicillin have been reported by various groups of investigators.[6,8–10] A variety of other reactions have been reported, namely, serum sickness syndrome;[12] Arthus phenomenon;[13,14] purpura with visceral envolvement;[15,16] periarteritis-like reaction;[17] papulovesicular eruption[18] and contact dermatitis.[19] These reactions have been induced by hypodermic, oral, topical and aerosolization routes.[18]

The purpose of this communication is to present another case of fatal penicillin anaphylaxis, with necropsy report, together with a group of cases selected to illustrate some of the nonfatal penicillin dermatoses. The management of acute penicillin reactions will be discussed.

CASE REPORTS

CASE 1.† A seventy-eight year old white female was admitted to the hospital with a severe hemorrhagic bullous dermatitis involving the mucous membranes of the mouth and skin of the lips, chest and thighs. Two weeks prior to her admission she developed a sore throat, chills and fever. Her private physician administered 400,000 units of penicillin intramuscularly and prescribed 20 oral tablets (50,000 units per tablet) one to be taken every three hours. The symptoms of her acute respiratory infection subsided in about ten days. Just about that time she noticed a progressive decrease in her sense of well being. Eight days following the last dose of penicillin the patient noticed hemorrhagic bullae appearing on various parts of her body. She felt chilled and feverish. The principal facts in the past history were decreased exercise tolerance, exertional dyspnea and angina after walking several blocks.

Examination revealed a grade IV retinopathy with conjunctivitis and blepharitis. The eyelids were covered with a yellowish secretion which was partly crusted. The mucous membrane of the mouth showed numerous hemorrhagic bullae of various sizes, some having already ruptured leaving raw bases. Similar bullae were noted on various areas of the body, particularly marked on the arms and thighs. The lungs presented numerous coarse rales and rhonchi which cleared partially with coughing. The heart was enlarged, the rate rapid and irregular. There were no abdominal findings. The reflexes were within normal limits. The temperature was 99.2°F., pulse 90 and respira-

† Permission was granted by the private physician to use this case in the present series.

* From the Department of Medicine, Northwestern University Medical School and Department of Pathology, Columbus Hospital, Chicago, Ill.

tions 20 per minute. The hemoglobin was 75 per cent, red blood cells 4.2 million per cu. mm., white blood cells 23,000 per cu. mm. with 80 per cent polymorphonuclears, 16 lymphocytes and 5 eosinophils. The urinalysis showed 3 plus albumin with an occasional red and white blood cell but no casts. The serum N.P.N. was 30.5 mg. per cent and the blood sugar 114 mg. per cent. The serum proteins were 5 gm. per cent with 2.9 gm. per cent albumin and 2.1 gm. per cent globulin.

A dermatologist who was called into consultation made the diagnosis of pemphigus vulgaris. The patient was treated with stovarsol, crude liver extract and tannic acid sprays administered to the raw areas. Her condition became progressively worse. On the fourth hospital day she was given 100 units of ACTH (acthar®) and 25 mg. cortisone four times daily. Within twenty-four hours the patient began showing some improvement. Two days later some of the bullae revealed early signs of infection and the patient was given 400,000 units of duracillin.® The same morning her condition became worse. Her pulse was rapid and irregular, the respirations labored and new crops of bullae began to appear on fresh sites. However, penicillin with large doses of cortisone and ACTH continued to be administered for the next ten days with neither improvement nor deterioration of the patient's condition. Terramycin (oxytetracycline) was substituted for penicillin and once again the patient began to show remarkable improvement within the next forty-eight hours. Her appetite, sense of well being and strength improved to the point where she was able to feed herself and sit on a chair for several hours of the day. The hemorrhagic bullae showed rapid resolution. On the twenty-fifth hospital day the patient developed a thrombophlebitis of the left popliteal vein. Unfortunately the patient's penicillin sensitivity was not recognized and 400,000 units of penicillin G was ordered, which was administered at 10:00 A.M. The nurse reported that within the next hour the patient became apprehensive, felt faint and was unable to take her medication. Her pulse became very rapid, irregular and almost imperceptible. The respirations were labored, while the blood pressure fell precipitously. She quickly lapsed into shock and expired.

Necropsy. Section through a bulla revealed distended blood vessels with edematous endothelium and perivascular lymphocytic and plasmocytic infiltration. In some areas there was extensive extravasation of blood into the subcutaneous layer. Section of the heart showed distended blood vessels, thinned and partially fragmented myocardial fibers with poorly stained nuclei. Although the coronary vessels showed an extensive arteriosclerotic process, no fresh thrombus was found. The dominant picture was that of a serous myocarditis and brown atrophy of the heart. Sections of the lung showed emphysema, pulmonary edema and a focal bronchopneumonia. There was no pulmonary embolus. Liver sections revealed central zone necrosis with a dense red cell infiltration. The surrounding hepatic cells, especially at the periphery of the lobule, had undergone fatty degeneration and vacuolization. The portal branches and the sinusoids were markedly congested and the Kupffer cells appeared to be hypertrophic. The picture was representative of fatty degeneration and central necrosis.

CASE II. A thirty-two year old white male was admitted to the hospital with severe urticaria, joint swelling and pain. He had been treated for acute otitis media with oral penicillin. Two weeks following the last dose he developed a severe allergic reaction. Five years previously he received a course of penicillin therapy for viral pneumonia without reaction. The patient had no known allergies.

On examination, his face was markedly swollen with such extensive periorbital edema that he was unable to open his eyes. The tongue was edematous but of normal color. The patient had a sense of suffocation on taking deep breaths. The left hand, wrist and fingers were edematous and painful on motion. The skin of the rest of the body revealed numerous urticarial lesions. The temperature was 100°F., pulse 100 and respirations 22 per minute. The heart, lungs and abdomen revealed no pathologic findings. Blood and urinalysis were within normal limits.

The patient was given a liquid diet and the following medication: epinephrine, (1:1000) 0.3 ml. subcutaneously every half hour for the first two hours; ephedrine sulfate, 25 mg. orally four times daily; demerol (meperidine hydrochloride), 100 mg. subcutaneoulsy three times daily and before bedtime; and 50 mg. cortisone subcutaneously twice daily. Antipruritic lotions were prescribed for skin comfort. After twenty-four hours only the cortisone and demerol were given twice daily. The patient's symptoms were under control within a few hours following

institution of therapy. The edema of the face began to recede by the next day. The swollen and painful joints of the upper extremity showed marked improvement within thirty-six hours. As the swelling of the left wrist subsided, swellings appeared in the left knee, ankle, right hand and knee, in the order named, but with minimal pain. By the fifth hospital day the swelling of all joints had disappeared. On the fourth day ACTH (acthar) was administered in 50 unit doses twice daily for two days, cortisone having been discontinued. The patient left the hospital on the sixth day.

CASE III. A sixty-five year old white male was admitted to the hospital for a prostatectomy and hernioplasty. His only complaint was referable to his genitourinary system. The hernioplasty was performed first and after three days transurethral resection of the prostate was performed. The patient received 400,000 units of penicillin daily. Convalescence for the next ten days was uneventful. He then began to complain of mounting emotional tension and a progressive intense pruritus which was followed by a generalized erythematous rash. Within twenty-four hours his entire body, including the palms of his hands and soles of his feet, was involved in an intense erythematous and urticarial reaction. The face was moderately edematous and the extremities only slightly swollen. His temperature mounted to 102°F., pulse 110, respirations 28 per minute. The peripheral blood showed an unusually high white count of 54,400 per cu. mm. with 46 segmented, 5 unsegmented polymorphonuclear leukocytes, 30 lymphocytes, 2 monocytes, 1 eosinophil, 1 myelocyte and 2 metamyelocytes. The hemoglobin was 66 per cent and red blood cells 3.5 million per cu. mm. Antihistamines afforded no relief of his symptoms. He received 0.3 ml. epinephrine (1:1000) every four hours, ephedrine sulfate 25 mg. orally three times daily; topical antipruritic; demerol (meperidine hydrochloride) 100 mg. intramuscularly twice during the day and once before bedtime and 50 mg. cortisone four times daily. The pruritus subsided within twenty-four hours. Cortisone therapy was continued for one week. As the erythema subsided, desquamation set in with the skin of the palms and soles shedding in large sheets. Within a week, the white count fell to 24,000 per cu. mm. and in ten days to a normal count. He was free of symptoms in two weeks following cortisone therapy.

This patient had received a course of penicillin therapy for a respiratory infection a year ago without reaction.

CASE IV. A forty-four year old white housewife was admitted to the hospital complaining of urticaria and purpuric skin lesions of three days' duration. The patient had received one injection of penicillin G two weeks prior to her admission. She first noticed a severe burning and itching sensation of the skin of the arms and hands. Three days later purpuric spots and hemorrhagic blisters appeared over these areas. Pyribenzamine afforded her no symptomatic relief. The lower lip and tongue became swollen and painful. There was no history of previous drug sensitivity although she did receive penicillin on previous occasions. Three years before she suffered a coronary occlusion with left ventricular failure but made a good recovery. On admission physical examination disclosed the following pertinent findings: Temperature 101°F., pulse 115, respirations 22 per minute. There was marked periorbital edema. The tongue was swollen, tender and showed a number of hemorrhagic macules. There was no lymphadenopathy. The heart was enlarged with a regular sinus rhythm and rapid rate. The lungs were comparatively clear. Blood and urinalysis were within normal limits. The patient received conservative supportive measures and 50 mg. cortisone given four times daily for six days. She made an uneventful recovery within four days.

CASE V. A seventy year old white female was admitted to the hospital with acute cholecystitis and cholelithiasis of three days' duration. As part of the treatment she received 400,000 U. penicillin intramuscularly, daily. One week following the first injection she developed an intense urticaria and erythema. The face and arms were moderateiy edematous. The joints were not involved. The patient had been treated for arteriosclerotic and hypertensive heart disease for many years. During her present penicillin reaction there was no evidence of congestive heart failure at any time. Serial electrocardiograms showed no deviation from her pre-admission tracings. Antihistamines afforded little relief of her symptoms. She received 50 mg. of cortisone five times daily for the first two days, then twice daily. Demerol, in 100 mg. doses was administered intramuscularly twice daily and ephedrine sulfate, 25 mg., was given three times daily. Complete control of the symptoms was achieved within twenty-four hours. Treatment was continued for a week. She left the hospital

two weeks following her admission with complete disappearance of her gallbladder symptoms. Cholecystectomy was not performed because the patient was considered to be a poor risk in view of her extreme obesity and cardiovascular status. While at home she complained of pruritus and urticarial lesions began to reappear on her back and face. She received 50 mg. cortisone orally twice daily and 100 mg. demerol orally before bedtime. She responded well and the treatment was discontinued after one week.

CASE VI. A twenty-four year old white female complained of pain and swelling of the eyelids of two days' duration. One week previously she had developed a mild blepharitis for which she used ophthalmic penicillin ointment. She claimed that as the inflammation of the eyelids subsided she experienced an itchy sensation and this was followed by progressive swelling of the lids. Several years ago, she received intensive penicillin treatment for infectious mononucleosis and had a mild penicillin reaction at that time. The patient was otherwise in good health. Physical examination and routine laboratory tests revealed no abnormalities. She was treated with oral cortisone in 50 mg. doses twice daily for one week and made an uneventful recovery. The possibility that the reaction may have been due to a chemical dermatitis was not excluded entirely.

COMMENTS

Clinical experience and experimental observation have indicated that crystalline penicillin possesses antigenic properties comparable to those of other crystalloids as reported by Rich.[20] It is generally believed that simple inorganic or organic chemical compounds, including those with the structural characteristics of antibiotics, may combine as a hapten with serum albumin to form a complex capable of participating in antigen-antibody reactions. Thus Tompsett et al.[38] have shown by dialysis experiments that 50 per cent of penicillin G, X and F, and about 90 per cent of penicillin K combine with serum albumin. It has been suggested that since penicillin K has a larger aliphatic group and hence greater binding capacity with albumin. this would explain its relatively decreased antimicrobial activity *in vivo* and the error involved in its assay in high serum dilutions.[39]

In the early era of penicillin therapy it was believed that the allergic reactions encountered were due in the main to impurities present in the commercial preparations. With the advent of crystalline penicillin similar allergic manifestations were observed however, thus implicating the penicillin molecule itself. In a few instances the procaine used in modified penicillin preparations was shown to be an independent sensitizing agent.[2] The inherent property of the penicillin G molecule to form an antigen in the body was attributed at first to its benzyl side chain; thus Volini and co-workers[22] reported that penicillin O, which has an allylmercaptomethyl side chain, was devoid of antigenic properties and could be used in patients sensitive to penicillin G. However, more recent studies have shown that penicillin O is as antigenic as penicillin G.[7,23] The impression gained from laboratory studies of the reactivity of penicillin and protein[38] is that as soon as penicillin enters the blood stream and is bound to serum albumin molecules, the stage is set for operation of the immune mechanism.

There is a marked individual variation among patients to penicillin sensitization. Why penicillin should have a high sensitizing potential in some individuals and not in others is still obscure. In the majority of the cases allergic to this antibiotic there is no obvious inherited familial tendency to allergy. It was shown by Cooke[26] that a large percentage of the population may develop a physiologic response to foreign proteins if given in excessive doses. About 90 per cent of the population can thus become sensitized.[27] Penicillin and other biologic material in excessive dosage may induce such a physiologic response.[24] It is well known that the same antigen may produce a wide variety of allergic manifestations in different individuals[25] and clinical observations indicate that this is true of penicillin. The underlying mechanism that determines these differences is obscure but hereditary factors may play some role.[25] Skin-sensitizing antibodies have been demonstrated in the serum of penicillin-sensitive individuals by employing the passive transfer technic and the intracutaneous test;[7,28] however, these antibodies are not always demonstrable in every case allergic to penicillin. Sherman[29] has pointed out that neither the skin test nor passive transfer can be used as a reliable clinical index of penicillin sensitivity. Positive skin reactions may occur in non-sensitive individuals and there may be a complete absence of any reaction to intradermal injection in known penicillin-sensitive patients.[12]

The antibody produced during the immune reaction inducing anaphylactic shock is a smooth

muscle-sensitizing antibody[40,42] and is immunologically distinct from the skin-sensitizing antibody produced during the serum sickness type of reaction characteristic of most penicillin hypersensitiveness. Recent studies of the immune mechanism in guinea pigs[37] have offered convincing evidence of the individual characteristics of these two types of antibodies. Furthermore, the presence of these two immune bodies has been demonstrated in the same sera of patients sensitized to foreign non-bacterial protein and to various drugs.[24,41] It would appear then, though not proved conclusively, that in penicillin anaphylaxis two distinct antibodies are present in varying concentrations: a skin-sensitizing antibody which reacts with intracutaneously injected penicillin or a product derived from penicillin and tissue protein causing the positive skin reaction noted in penicillin anaphylaxis; and an anaphylactic antibody responsible for the major clinical features, namely, smooth muscle spasm and depression of vasomotor tone. Reports of the Arthus reaction[13,14] and the periarteritis reaction[17] in penicillin hypersensitivity would suggest the production of a third type of antibody, namely, precipitating immune body. It has been pointed out by Raffel[42] that the gross physiologic and anatomical changes characteristic of the Arthus reaction are produced by the interaction of high concentrations of precipitating antibody and antigen. It should be made clear, however, that while there is ample evidence for the presence in man of a skin-sensitizing antibody, the existence of smooth muscle and precipitating antibodies still awaits experimental proof.

Case 1 of the present series had no history of asthma or of any allergic reactions. She had received one parenteral dose and twenty tablets of oral penicillin. About two weeks later she developed a severe penicillin reaction characterized by a hemorrhagic bullous dermatitis which unfortunately was not recognized as an allergic manifestation and was treated as pemphigus vulgaris. It is of interest that when the patient was receiving large doses of cortisone while on penicillin therapy, her condition showed little progressive change. Apparently the adrenocorticoids, while having no demonstrable depressing effect upon penicillin antibody synthesis or upon the union of antibody and antigen, in the therapeutic doses employed, nevertheless did prevent further damage at the cellular level.[30] When terramycin (oxytetracycline) replaced penicillin, marked improvement was evident within twenty-four to twenty-eight hours. The skin lesions gradually disappeared within several weeks and no new ones were formed. The patient's general clinical condition improved remarkably. From the time penicillin was discontinued to that of the last administered dose, a period of three weeks elapsed. It is conceivable that during this interval a progressive increase of anaphylactic antibodies had occurred, so that the final dose of 400,000 units of penicillin was more than sufficient to cause shock and death. It is of further interest to note that although the patient was maintained on 100 mg. of cortisone up to the time of her death, the hormone was incapable of averting the fatal outcome. It is believed that the overwhelming release of histamine from injured tissue cells caused by the antibody-antigen reaction may be the basic factor causing the peripheral vascular collapse and respiratory signs.[25] It is known that severe anaphylactic shock and immediate death are more likely to occur in guinea pigs by introducing the sensitizing antigen intravenously.[31] Whether penicillin was injected accidentally into the patient's blood stream cannot be ascertained in this case.

Necropsy of this case disclosed no pathologic evidence of acute coronary occlusion or pulmonary embolus to explain the immediate cause of death. Examination of the skin failed to substantiate the clinical impression of pemphigus vulgaris. The lungs were distended by an emphysematous process and the parenchyma revealed pulmonary edema. Microscopic examination of the myocardium showed moderate, extensive serous myocarditis with round cell infiltration. The liver revealed moderate central necrosis and the kidney a mild interstitial nephritis. Longcope[32] demonstrated extensive inflammatory reaction in the myocardium and liver following injection of an antigen into sensitized animals. These consisted of areas of degeneration and infiltration with round cells, which in the heart were scattered throughout the myocardium and in the liver were usually situated about the portal spaces. These changes occurred after a period of ten to twenty-one days, providing sufficient time for the animal to produce excessive anaphylactic antibodies. Harvey[25] pointed out that in the anaphylactic type of reaction profound changes occur in the vascular endothelium causing increase in permeability, necrosis and hemorrhage.

MANAGEMENT

The management of penicillin hypersensitivity reactions consists of: (1) treatment of anaphylactic shock, if present; (2) suppressing the tissue response to the antibody-antigen reaction and (3) supportive measures for the comfort of the patient. The peripheral vascular collapse in anaphylactic shock is a grave medical emergency with potentially fatal outcome. The immediate aim is to raise the depressed vasomotor tone and to relieve the intense bronchial muscle spasm. Epinephrine (1:1000) is the drug of choice because of its rapid action and availability. It is administered intravenously in a dose ranging from 0.2 to 0.3 ml., with extreme caution. Since the pressor action of epinephrine is of short duration, repeated injections may be required to raise and maintain the blood pressure above shock level during the initial critical period. At times the depressed vasomotor tone may be relieved for a short period only, even with repeated injections of epinephrine. In this situation L-arterenol (levophed®) given as a continuous infusion drip may be used with striking results. Unlike epinephrine, L-arterenol has minimal effect upon the myocardium and ventricular rate, produces less central nervous system stimulation and is about eight times less toxic.[35] The infusion solution is prepared by adding 4 mg. (4 ml. of 1:1000) of L-arterenol to 500 ml. of 5 per cent glucose or normal saline. The rate of infusion drip is regulated by the pressor response. Larger concentrations (8 mg.) of arterenol may be required in some instances of shock when the response to the pressor amine is too slow. Striking potentiation of the blood pressure response may be achieved by simultaneous administration of cortisone.[36] It has been shown that the adrenocortical hormone restores normal reactivity of the blood vessels to both endogenous and exogenous L-arterenol.[35] The bronchospasm is relieved with intravenous aminophylline (0.25 to 0.5 gm. in 100 ml. saline) which should be given slowly and cautiously in the presence of peripheral vascular collapse. Oxygen or oxygen-helium mixtures may be required in some cases to relieve the cyanosis.

In the serum sickness type of penicillin reaction characterized by urticarial or erythematous skin eruption, lymphadenopathy, pruritus, fever and usually edema of the eyelids, face and ankles, therapy is aimed at controlling the swelling, suppressing the antibody-antigen reaction and keeping the patient comfortable. Subcutaneous injections of epinephrine (1:1000), in a dose ranging from 0.3 to 0.5 ml., are administered every two to four hours for several injections to control the acute stage of urticaria and angioneurotic edema. Twenty-five mg. of ephedrine sulfate given orally four times daily is of some value in controlling the edema. The antibody-antigen reaction is suppressed with either 100 units of ACTH (acthar®) or 200 mg. cortisone given in four divided doses, daily. There is very little difference in the beneficial therapeutic effect obtained with either hormone.[33] The effectiveness of these hormones in acute self-limited allergic reactions, especially in penicillin hypersensitivity, has been dramatic;[12,34] they prevent development of new lesions while allowing spontaneous regression of old ones. In the present group of cases cortisone was used until all allergic manifestations had subsided and then was continued for two extra days. In some cases when cortisone was used for more than one week, ACTH (acthar) was employed in a dose of 100 units daily for two days to avoid possible atrophy of the adrenal cortex. About 50 per cent of the cases had recurrences of mild urticaria within a week or ten days following the last dose of cortisone, which has been the experience of others.[34] This is to be expected in some cases since it has been shown[30] that cortisone has a limited effect upon suppression of antibody synthesis or elimination of antibody from the body. In some instances of recurrence of urticaria a second course of 50 mg. oral cortisone was prescribed daily for one week; complete remission followed within a week of therapy. Antihistamines proved of little value in our experience as well as that of others.[12] Demerol (meperidine hydrochloride) administered intramuscularly had a distinct therapeutic benefit in providing comfort for the patient, especially at night. In a number of the patients weakness and easy fatiguability were common complaints following alleviation of the visible allergic manifestations. Case III complained of lassitude, extreme fatigue and general skeletal muscular weakness following minimal effort. He was treated with neostigmine bromide. The results were so gratifying that two subsequent patients were treated with the same drug with equally good effect. The cause of the asthenia in this post-allergic state is not yet clear. The use of neostigmine is mentioned here with the hope

that it may be tried by others in the treatment of similar cases.

PREVENTION

The general impression gained from the numerous reports appearing in the medical literature is that induction of penicillin hypersensitivity in the general population is on the increase. More and more persons are being sensitized unjustifiably and uselessly in illnesses for which a subcutaneous injection of normal saline might have proved just as efficacious. Penicillin is a valuable and potent antibiotic in certain well defined infections and should be reserved for only such indications. There is as yet no simple technic of predicting a reaction in previously penicillin treated patients. Dr. Feinberg and his associates[7] have made some valuable suggestions for decreasing the incidence of these reactions.

SUMMARY

A case of fatal penicillin anaphylaxis with necropsy findings is presented. Outstanding pathologic features were serous myocarditis with round cell infiltration, pulmonary edema, emphysema and general vascular endothelial necrosis.

Shock in penicillin anaphylaxis is treated immediately with epinephrine administered intravenously. When the blood pressure cannot be maintained above shock levels with epinephrine the pressor amine of choice is L-arterenol administered as a continuous infusion drip. Cortisone is the drug of choice in treating penicillin allergic reactions; antihistamines have limited value.

The probable mechanism of the penicillin immune reaction is discussed.

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Review

Aetiology and Pathogenesis of Rheumatoid Arthritis*

ELLIS DRESNER, M.D., M.R.C.P. (London)†
New York, New York

THE aim of past attempts at an aetiologic classification of the rheumatic diseases has been to explain them on the basis of known pathologic mechanisms, toxic, infective, allergic, metabolic or psychosomatic, and in the past twenty years the demonstration of histologic similarities of the connective lesions of many of the diseases has led some observers to postulate a common pathogenetic basis for them all. So far no type of classification has proved successful; no known aetiologic cause has been proven, and the fundamental connective tissue lesion has been found not to be specific. The only justifiable reason at present for grouping these diseases together is the common site of their primary lesions in the connective and supporting tissues. Aetiologic and pathologic classifications proving unsatisfactory because of lack of knowledge of the former or of specificity of the latter, one can at present only assume the unity of the group on an anatomic basis and examine the known facts and the evidence for and against the various theories of the aetiology and pathogenesis of these diseases in an attempt to find which most accurately fits what is known of the natural history and pathology of the diseases.

In this paper the known facts and theories concerning the cause of rheumatoid arthritis and its relation to the other rheumatic diseases are reviewed.

GENERAL PATHOLOGY

The rheumatoid process is a general systemic one involving primarily mesenchymal connective tissue in many sites. The dominant feature is a chronic inflammation varying in intensity and extent with the clinical severity and laboratory manifestations of the disease. The cardinal histologic features are the formation of granulation tissue with destruction of more specialized elements, reparatory fibrosis, fibrinoid change and cellular infiltrations characteristically of lymphocytes and plasma cells. The distribution of these components varies from site to site and often in the same tissue; all may be present together. The lesions are by no means specific. Collins[78] considers that as the pathologic changes affect connective tissues limited in their potentialities for reaction none alone can be diagnostic, but taken together they make a recognizable picture. He believes the initial change to be a proliferation of connective tissue followed by its degeneration, although others think that fibrinoid degeneration is the primary change and is followed by mesenchymal proliferation and cellular infiltration. Gibson[140] agrees that although the tissue changes in rheumatoid arthritis have in themselves little specificity, their association in joints, subcutaneous tissues, heart, nerves and elsewhere is sufficiently constant to be characteristic. He stresses the histologic pleomorphism of the rheumatoid process, and regards the cellular aggregations of Allison and Ghormley in the synovia, and the subcutaneous necrobiotic nodule, as being the most distinctive features of the tissue changes, and of diagnostic significance. In general, the pathology of rheumatoid arthritis differs quantitatively rather than qualitatively from that of other chronic inflammatory diseases.

Rheumatoid Nodules. Subcutaneous nodules occur in about one-fifth of all cases of rheumatoid

* From the Department of Medicine, and the Study Group on Rheumatic Diseases of New York University College of Medicine, New York, N. Y. Supported in part by funds from the Masonic Foundation for Medical Research and Human Welfare, and the Arthritis and Rheumatism Foundation (New York Chapter).

† Fellow of the Dazian Foundation for Medical Research.

arthritis, most commonly at pressure points, this distribution being related to local trauma. Beginning as a proliferation of vascular granulation tissue, they become surrounded by lymphocytic infiltrations. Fibrosis occurs centrally, while mononuclear cells collect at the periphery. Fibrinoid degeneration then takes place at the centre. In the fully developed nodule a central area of fibrinoid has at its margins a palisade of radially aligned fibroblasts from which reticulin fibrils pass into the central zone, and is surrounded by a dense layer of avascular collagen constituting the main bulk of the nodule. Connective tissue destruction is the dominant feature of the mature nodule, in contrast to the proliferative and erosive pannus formation in the synovia.[33] Sokoloff and his coworkers believe that a focal necrotizing arteritis is the starting point of the rheumatoid nodule and that this is but a local manifestation of a generalised, specific, rheumatoid arteritis.[380,382] Attempts to produce nodule formation artificially in subjects with rheumatoid arthritis by various measures have proved uniformly unsuccessful.[353]

Extra-articular Lesions. Of recent years increasing study has been made of the non-articular lesions of rheumatoid arthritis. That the heart is frequently involved by granulomatous lesions is now well established as the result of necropsy studies, these lesions generally not being manifest clinically. Adhesive pericarditis is the common finding, and granulomatous lesions, histologically distinct from those of rheumatic fever, and similar to the granulomatous inflammation of the rheumatoid subcutaneous nodule, occur in the valves and myocardium. In addition, valvular lesions indistinguishable from those of rheumatic fever, and not giving rise to clinical heart disease, are found at necropsy in an appreciably higher proportion of rheumatoid arthritics without a history of past rheumatic infection than in control subjects. Whether they represent an increased predisposition of rheumatoid subjects to the development of "silent" rheumatic carditis or whether they are really stigmata of rheumatoid arthritis is at present a matter of some controversy.[30,52,122,147,340] A specific type of rheumatoid aortitis has also been described.[27,32]

Perivascular inflammatory lesions are found in the striated muscles of about 75 per cent of patients with rheumatoid arthritis[85,188,216,383,393] but have no special diagnostic features and resemble similar lesions occurring in myasthaenia gravis, and in disseminated lupus, dermatomyositis and other connective tissue diseases. Russell[342] is of the opinion that in both myasthaenia gravis and rheumatoid arthritis the muscular changes are of importance in relation to the clinical evidence of muscular dysfunction. The same sort of lesions have also been found at autopsy in subjects dying of non-rheumatic conditions, the incidence varying from 4.2 to 13.5 per cent according to the muscles sampled.[71] Nevertheless they are quantitatively more numerous in rheumatic than in non-rheumatic conditions. "At whatever point the rheumatic diseases are approached by the histologist, quantitative considerations in relation to non-specific reactions arise."[140] Degenerative changes in muscles, sometimes extensive enough to cause rupture, have also been described.[213]

Perineural granulomatous lesions of peripheral nerves occurring in rheumatoid arthritis were first described by Freund and others[129] and are identical in their microscopic structure with the necrobiotic nodules and synovial lesions. Morrison et al.[269] found perineural lesions in 75 per cent of samples of nerve tissue from the spinal cord and sympathetic ganglia of rheumatoid patients. Similar rheumatoid lesions occur in tendon sheaths[10,209] and a non-necrotizing angiitis has also been described in muscle arterioles.[97] Motulsky and his colleagues[270] describe a giant follicular hyperplasia in the lymphadenopathy of rheumatoid arthritis. Ocular manifestations are not uncommon. The most frequent is a uveitis taking the form of recurrent, acute, bilateral iritis, occurring in up to 4.7 per cent of cases.[33] Other manifestations noted are episcleritis, choroiditis, keratoconjunctivitis sicca (Sjögren's syndrome,[181,375]) and scleromalacia perforans.[407,409] The latter is essentially a necrobiotic nodule in the sclera and may cause loss of sight.

"Rheumatoid" changes have been described in the lungs by Ellman and Ball[110] in three cases. Histologically the lungs showed interalveolar fibrosis and fibrinoid necrosis with mononuclear cell infiltrations. Similar cases have also been described by Leys and Swift[239] and by Bloom and Rubin.[38] In their study of the visceral lesions of rheumatoid arthritis Baggenstoss and Rosenberg[20] failed to find any specific changes in the lungs of thirty patients coming to necropsy, although the presence of adhesions in three-quarters of the cases suggested that the pleura is commonly involved. Caplan[55] has recently found

a relation between rheumatoid arthritis and massive radiologic lung changes in patients exposed to pneumoconiosis but the significance of this relationship is undetermined. It is suggested that a deficiency of adrenocortical hormones may underlie both the arthritis and a modified response of the lung tissues to dust and infection in these cases.[265] There is no clear evidence as yet that any of the lung changes described in association with rheumatoid arthritis are a specific manifestation of the disease.

AETIOLOGIC PREDISPOSING AND PRECIPITATING FACTORS

Various factors have been suspected of predisposing to or precipitating the onset of rheumatoid arthritis. The predeliction of the disease for females and its frequent onset in early middle age are well known, although figures for sex incidence and age of onset vary a little due to selection differences in the cases studied. A definite familial tendency to rheumatoid arthritis is noted by Ragan[310] and by Stecher et al.[391] Anthropometric studies by Seltzer[359] claim to show pronounced anthropologic differences between men and women with rheumatoid arthritis and those with degenerative arthritis. Emotional factors, the menopause, preceding infection especially of the upper respiratory tract[296,354,377] and trauma[238,243] have all been thought to have a significant influence in determining the onset of the disease but all such studies of aetiologic factors have usually been based on clinical impressions and on statistically uncontrolled material. In 1950 the Empire Rheumatism Council[113] instituted a controlled investigation to examine the various claims regarding the importance of certain factors alleged to be of aetiologic significance in 532 subjects with rheumatoid arthritis and paired controls, and subjected their findings to statistical analysis. The results went far to refute many long-conceived fallacies. The sex ratio of the cases was 162 females to 100 males, and the mean age of onset was forty-two years for the men and forty-one years for the women. Psychologic precipitating factors, previous illnesses, preceding infections, personal and family histories of allergic disorders, focal sepsis, home conditions, pregnancy, parturition and menstrual history were all found to have no statistically significant relationship to the onset of the disease. On the other hand, a familial history of arthritis, exposure to cold preceding the onset, and the presence of peripheral circulatory disorders before the onset were all found to occur in a statistically significant majority of the rheumatoid patients. These factors merit further consideration. A similar statistical survey of 293 cases by Short, Abrams and Sartwell[371] came to very similar conclusions.

THEORIES OF INFECTION

Focal Sepsis. Focal sepsis has occupied a larger part in theories concerning the aetiology of rheumatoid arthritis than in any other disease, and the concept is by no means yet abandoned. Lansbury[228] for instance believes that "from a practical point of view . . . we are not yet ready to ignore focal infection in rheumatoid arthritis." There is a truly immense literature on septic foci as an aetiologic factor in, or as the actual cause of, rheumatoid arthritis, with many enthusiastic claims for the beneficial results of their removal. Practically no site in the body has not been alleged to be a source of infection and the cause of arthritis. Bockus[39] and Gauss[134] consider chronic biliary infection as the cause of arthritis. Cmunt[73] and Weber,[426] among many others, blame infected teeth. Hamblen-Thomas,[165] McCollom[258] and Williams and Slocumb[430] hold sinus infections to be the responsible agent, while Robinson and Robinson[334] believe that most cases of rheumatoid arthritis in women are due to chronic cervicitis, and Coleman and Capps[76] thought rheumatoid arthritis could result from diverticulosis of the colon. The finding of multiple foci of infection in 58 per cent of 343 cases of rheumatoid arthritis is reported by Thompson, Wyatt and Hicks,[403] and similar or higher figures are given by other authors. That the joints and related structures remain sites of secondary metastatic foci after the original septic foci have been removed has recently again been suggested.[212] In 1927 Cecil and Angevine found the majority of 200 rheumatoid patients to have one or more infectious foci, but ten years later 70 per cent of 200 new patients had no demonstrable infection. To evaluate the role of focal sepsis they attempted to create infected foci in rabbits, of which 85 per cent developed arthritis when given a strain of haemolytic streptococci intravenously. Only 11 per cent developed arthritis when given the same strain intramuscularly and in large amounts, and the authors concluded that although focal infection can cause rheumatoid arthritis, it does not account for all cases.[62,63] Davidson[87] has

summarised the evidence for and against the focal infection theory.

The great majority of the reported studies are uncontrolled observations lacking statistical validity although there have been a few attempts to show that focal infection is just as common in patients with non-rheumatic diseases.[44] Davidson and his colleagues[88] have recently made a careful study of the presence of focal infection in the upper respiratory tract in 100 unselected patients with rheumatoid arthritis and 100 non-rheumatic controls in order to see whether any support could be gained for the theory that focal infection is the means whereby the tissues become sensitized to bacterial antigens, further contact with which may provoke an abnormal immunologic response. The results are illuminating. Forty-four per cent of the rheumatoids and 43 per cent of the controls had infection in the upper respiratory tracts, the anatomic distribution of these foci being practically identical in the two groups.

"Autointoxication" from the bacterial flora of the large bowel was a popular conception of the cause of rheumatoid arthritis with a vogue in the 1920's, and led to the use of colonic lavage and colectomy as therapeutic measures. This almost forgotten theory still has its advocates.[19,25,424]

There is no good evidence that focal infection is of any significance in the development of rheumatoid arthritis.

Streptococcal Infection. The clinical course of rheumatoid arthritis in many ways resembles that of a chronic infection and not unnaturally intensive search has been made for a causative organism. One of the earliest studies of this nature was that of Bannatyne et al.[24] in 1896, who first reported the recovery of "a minute bacillus exhibiting marked polar staining" from twenty-four of twenty-five specimens of synovial fluid from rheumatoid arthritics, and from the blood of some of the patients. These workers regarded their findings as conclusive but the organism was not further identified. In 1929 Cecil and his colleagues[66] claimed to have found a typical strain of haemolytic streptococcus in the blood of forty-seven of seventy-eight rheumatoid arthritics. Gray and Gowen[149] confirmed the reports of Cecil, finding the blood or synovial fluid positive for the "typical strain" in 62 per cent of seventy-one patients, and claiming that specific vaccine therapy "cured or improved" many of their cases. They also found agglutinins to the "rheumatoid" streptococcus in the sera of most of their patients. Wainwright[416] claimed a high percentage of positive blood cultures in cases of rheumatoid arthritis, and found that most patients benefited from intravenous streptococcal vaccine. Margolis and Dorsey[251,252] also thought the streptococcus aetiologically significant, although they isolated a non-haemolytic streptococcus only infrequently from the blood and joint tissues, and not at all from the synovial fluid of cases of rheumatoid arthritis. However Dawson et al.,[91] using the technique of Cecil, failed to find organisms of aetiologic significance in the blood, synovial fluid or subcutaneous nodules of eighty rheumatoid cases. Further negative studies were reported by other workers.[36,77,126,259] Later, after extensive cultural and inoculation studies, Cecil retracted his previous report of 1929, admitting the probability of contamination.[8,9]

Experimental Streptococcal Arthritis. Experimentally, streptococci can produce in rabbits an acute haematogenous polyarthritis, later becoming chronic, simulating rheumatoid arthritis in man. Bannatyne et al.,[24] as long ago as 1896, produced such a polyarthritis in rabbits by intravenous inoculation with the organism they isolated from the joint of patients with chronic arthritis, and noted the pathologic resemblance to the lesions of human rheumatoid arthritis. In 1913 Jackson[196] gave a detailed account of the chronic joint lesions caused by the intravenous inoculation of rabbits with various strains of streptococci. Cecil, Nicholls and Stainsby[66,67] noted the resemblance of the lesions they produced experimentally in rabbits with their "typical strain" of streptococci to those of human rheumatoid arthritis. The reproducibility of chronic arthritis experimentally with these streptococci, together with the finding of a high titre of agglutinins to the organism in the blood of rheumatoid patients, was taken by them to be direct evidence of the streptococcal aetiology of the disease. Later[64] they showed that rabbit arthritis could be caused by a variety of streptococci in addition to that isolated from rheumatoid arthritics, and concluded that the type of disease from which the streptococci were isolated bore no relation to their capacity to cause arthritis. They also found that a Staphylococcus aureus, a pneumococcus and Bacillus paratyphosus A could cause similar lesions when injected intravenously. In all the experiments the infecting organism was recoverable from the joints, and the disease was accompanied by constitu-

tional symptoms of infection. The organisms used produced uniform histologic changes in the synovia consisting of cellular infiltrations, increased vascularity and synovial proliferation as in rheumatoid arthritis. Hadjopoulos and Burbank[158] had previously succeeded in producing a chronic polyarthritis by the same technique using ten different strains of streptococci isolated from the blood of cases of chronic arthritis, and after examining the lesions in detail had found them to correspond exactly with those of human rheumatoid arthritis. They found, however, that their organisms were not specific for the joints but caused lesions in the internal organs as well, notably the liver and kidneys. From these, as well as from the joints, "arthrotropic" streptococci could be recovered. Hedlund and Lofstrom[174] confirmed these observations, showing that polyarthritis can be produced in rabbits by intravenous but not by intracutaneous injections of haemolytic streptococci, the lesions being accompanied by high serum levels of antistreptolysin.

Antistreptococcal Agglutinins and Serologic Precipitins. Mention has already been made of the finding of antistreptococcal agglutinins in the sera of rheumatoid patients. The first systematic study of this nature was that of Cecil, Nicholls and Stainsby[67] in 1931, who found that 96 per cent of 103 patients with rheumatoid arthritis had in their sera high titres of agglutinins to the "typical strain" of streptococcus, while none were found in the blood of normal controls. They believed this agglutination phenomenon to be ". . . quite as specific and reliable for differentiating [rheumatoid arthritis] as is the Widal test for typhoid fever." The fact that the agglutinins were also active against streptococci from erysipelas and scarlatina did not, in their opinion, detract from their diagnostic value. Nicholls and Stainsby[279] expanded these observations and noted that while 94 per cent of rheumatoid patients had serologic agglutinins to various haemolytic streptococci, they were never found in the sera of patients with degenerative arthritis, and so confirmed their diagnostic value. They concluded that the agglutinin was a specific antibody to an antigen common to many types of haemolytic streptococci. The presence in the sera of rheumatoid arthritics of haemolytic streptococcal agglutinins in high titre has since been widely confirmed,[92,93,149,199,204,416] and agglutinins active against R strains of pneumococci have also been found.[92,93] It is generally accepted that their presence bears a direct relationship to both the duration and the activity of the disease. They can also be detected in the synovial fluid of rheumatoid joints, often independently of their presence in the blood.[235] Cecil and de Gara[65] collated the observations of nineteen authors in over 2,000 cases and found the percentage of positive serum agglutination titres recorded varied from 36 to 97 per cent, with an average of 68 per cent of positive reactions.

The finding of antistreptococcal agglutinins in rheumatoid arthritis sera led to a search for the presence of other streptococcal antibodies. Myers and his colleagues[273,274] found significant titres of antistreptolysin O and antifibrolysin in the sera in proven haemolytic streptococcal infections and in cases of rheumatic fever, but none in rheumatoid arthritis. Perry[301] confirmed the absence of significant amounts of antifibrolysin from the serum in rheumatoid arthritis and ankylosing spondylitis, and Bunim and McEwen[48] found antistreptolysin O to be absent from rheumatoid sera even in the presence of high titres of haemolytic streptococcal agglutinins, the same strain of streptococcus being used to detect both antibodies. This was confirmed by Ouchterlony and Palmborg.[289] Streptococcal antihyaluronidase was investigated in the sera of rheumatoid patients by Harris and others[166] and by Faber[114] who found that, together with antihaemolysin, titres of this antibody were low in contrast to patients with rheumatic fever in whom titres were in proportion to those found in uncomplicated streptococcal infections.

In spite of the presence of haemolytic streptococcal agglutinins in high titre in active rheumatoid sera and the facility with which streptococci can be made to produce a chronic polyarthritis in the experimental animal simulating the morbid anatomy of rheumatoid arthritis, there exists considerable evidence against a streptococcal origin of the disease. This mainly concerns (1) the failure conclusively to demonstrate haemolytic streptococci in the blood, synovial fluid or tissues of patients with rheumatoid arthritis, these organisms always being recoverable from these sites in experimental rabbit arthritis; (2) the chronic course of the disease and its failure to respond to antibiotics; and (3) the absence of a significant rise in the content of fibrinolysin, streptolysin and other haemolytic streptococcal antibodies in the

blood. The summation of this evidence would appear to be conclusive in exculpating the streptococcus of any significance in the pathogenesis of rheumatoid arthritis, although not excluding streptococcal infection as one of the possible factors precipitating the onset of the disease or its recurrences. If this be so the presence of streptococcal agglutinins in the serum requires explanation, and this can only be that the phenomenon is a non-specific property of the serum of a non-antigenic nature. There is clear proof that this is so. Mention has been made of the observations of Dawson, Olmstead and Boots[92,93] that the agglutinins present are active against non-encapsulated strains of pneumococcus, and this is confirmed by Wallis.[420] Dawson, Olmstead and Jost[94] noted a tendency of rheumatoid sera to precipitate haemolytic streptococci parallel to their ability to agglutinate these organisms, and Chasis and McEwen[68] also found non-type-specific precipitins in rheumatoid sera active against crude streptococcal extracts, independently of the presence of agglutinins. Both these groups of workers thought the precipitins indicate the presence of non-type-specific antistreptococcal antibodies. Bruce and Caswell,[46] however, suggested that while they may be specific for rheumatoid arthritis, they are not aetiologically significant. Further light has been thrown on this problem by the demonstration of Wallis[419] that not only do the sera of many patients with rheumatoid arthritis have a tendency to precipitate spontaneously in saline solution, especially after centrifugation, but also that such sera, containing streptococcal agglutinins in high dilution, can agglutinate suspensions of fine collodion particles unsensitised by antigen. This collodion-agglutinating factor is often present in high dilutions but is not directly relatable to the titre of streptococcal agglutinins in the same serum. It is not found in normal sera in significant dilution, is destroyed by heat and appears to be carried by a globulin fraction of the serum. Wallis believes this to be a non-specific flocculation reaction analogous to the Takata-Ara, colloidal gold and cephalin-cholesterol reactions. All of these phenomena, including the tendency of rheumatoid sera to spontaneous precipitation in physiologic saline solution, appear to be related to an elevated plasma globulin content. It would therefore appear that there is an abnormal globulin in rheumatoid sera which probably exaggerates the action of naturally occurring precipitins for streptococcal and pneumococcal fractions and agglutinins for R strains of pneumococci, and enhances non-specifically the action of agglutinins to group A streptococci which may be present in nasopharyngeal carriers of this organism.[421]

Non-Streptococcal Infections. A chronic polyarthritis, clinically and pathologically resembling rheumatoid arthritis, can be produced in mice by the intravenous or intraperitoneal injection of a filterable pleuropneumonia-like organism originally isolated from the brain of a normal mouse. The arthritis is migratory, with fusiform joint swellings, and progresses to ankylosis. Organisms can be cultured from the joints several weeks after infection but the mice otherwise remain in good health. Pathologic changes are limited to the joints and consist chiefly of a proliferative synovitis.[344] Attempts to isolate L organisms from the blood, synovial fluid and tissues in cases of rheumatoid arthritis have proved uniformly negative,[9,118,130,307,345] although Wallerstein et al.[418] claim to have found agglutinins to one strain of L organism in the sera of two patients with Reiter's syndrome, and a similar claim has been made by Dienes et al.[98] At present evidence that these organisms are pathogenic for humans is still inconclusive.

A similar chronic proliferative polyarthritis, also with a remarkable resemblance to rheumatoid arthritis, can be caused in swine by intravenous inoculation with Erysipelothrix rhusiopathiae[79] but this organism does not cause arthritis in humans.

Attempts to isolate a possible causative virus from the blood and tissues in rheumatoid arthritis have so far proved unfruitful.[106,107] Gordon,[146] in a well reasoned argument from the bacteriologist's point of view, believes rheumatism to be of microbial origin at the ultramicroscopic level. He has observed the presence of elementary bodies in rheumatic tissues, and on this basis postulates a group of specific "rheumatic" viruses with a selective affinity for connective tissue. Levinsky and Lansbury[234] were unable to transmit rheumatoid arthritis from one human subject to another by direct transfer of rheumatoid synovial fluid but give reasons for believing that their negative results do not exclude the possibility of a viral aetiology for this disease. Bauer, Clark and Dienes[26] believe, from the failure of homologous rheumatoid nodule transplants to survive, that they are not due to living agents.

Definitive evidence that direct bacterial infection plays a primary role in the pathogenesis of rheumatoid arthritis is completely lacking, and no causal relationship between streptococcal infection and rheumatoid arthritis, such as is known to exist in rheumatic fever, can be demonstrated by clinical, bacteriologic or immunologic means. The experimental arthritis which can so readily be produced in animals by intra-articular or parenteral infection with microorganisms is not a valid counterpart of human rheumatoid arthritis, and the lesions produced thereby resemble human rheumatoid arthritis only by virtue of the very limited capacity that joint tissues have for reacting to any stimulus, whether bacterial or chemical. Agglutinating factors in rheumatoid serum for bacteria, erythrocytes and small particles are not antibodies, and are probably due to the presence of an abnormal globulin which in itself is a manifestation of the disease. That the mesenchymal lesions of rheumatoid arthritis may be due to an as yet undiscovered virus seems unlikely, but cannot at present be definitely excluded.

PSYCHOGENIC FACTORS

The proponents of an old neural theory of rheumatoid arthritis postulated that it is a nervous disorder, chiefly on the basis of the symmetric nature of the joint involvement. It has been a common practise to attribute the onset of rheumatoid arthritis or its clinical fluctuations to psychologic upsets, and Thomas[402] quotes Paulus Aegineta of the sixth or seventh century as having been the first to associate rheumatoid arthritis with emotional trauma. Many who have analysed the emotional states of rheumatoid patients have claimed that emotional trauma of one sort or another precedes and apparently precipitates the onset of the disease in all or nearly all cases.[61,74,291,377] The value of the great majority of such studies is limited by a lack of control studies in other, non-rheumatic, chronic diseases, but the impression has remained that emotional factors can influence the development of exacerbations and remissions in the course of the illness. The statistical survey of aetiologic factors in rheumatoid arthritis of the Empire Rheumatism Council,[113] already mentioned, found no significant relationship between psychic trauma and the onset of the disease.

Gregg[153] has made the interesting observation that psychotic individuals are strangely immune to rheumatoid arthritis, the incidence amongst 15,196 psychotic patients being only one-seventeenth of that of the population at large. He also found no case of rheumatoid arthritis in 3,000 autopsies on psychotics. He suggests that this immunity of psychotics is due to their protection from physical and mental trauma. Nissen and Spencer[280] also found no rheumatoid arthritis in 2,000 schizophrenics and believe the two conditions to be mutually exclusive, each representing a different mechanism whereby an inadequate personality escapes from reality.

The current concept of the existence of psychosomatic disorders has extended to the field of rheumatism, and there are some who would definitely classify rheumatoid arthritis as a psychologically conditioned illness.[164] Others deny this possibility.[40,372] Kellgren[208] has made some observations on the personality changes which are a common feature of rheumatoid arthritis, and which he believes are in the nature of a toxic psychosis and therefore an integral part of the disease process. While most observers are agreed that emotional disturbances bear a close temporal relationship to clinical fluctuations in the course of the disease, the theory that rheumatoid arthritis is of psychosomatic origin is not bourne out by the observations of most physicians.

THEORIES OF AVITAMINOSIS

Vitamin A. Many cases of rheumatoid arthritis are associated with low blood levels of vitamin A[109,162,308] and this may determine their increased susceptibility to infections of the upper respiratory tract;[356] but while the deficiencies can be corrected by the oral administration of the vitamin, this does not influence the arthritis.

Vitamin B Complex. Fletcher, in 1922,[123] suggested that a vitamin B deficiency might be related to the development of certain features of rheumatoid arthritis, largely on the assumption that there was a causal relationship between digestive disturbances and the development of arthritis. Steinberg[392] found abnormal bowel radiographs in many arthritic patients which he attributed to vitamin B deficiency, and postulated increased vitamin B requirements in arthritis. Although he found evidence of chronic vitamin B deficiency—dermatitis, glossitis and stomatitis—to be not infrequent in chronic rheumatoid arthritis, and these lesions responded to various vitamin B fractions, Freyberg[131] is of the opinion that, because the joint lesions are uninfluenced by correction of the deficiency,

there is no direct relationship between avitaminosis B and rheumatoid arthritis. Traeger[405] found none of the components of the B complex directly to influence rheumatoid arthritis, but observed the vasodilatory action of nicotinic acid to have a pronounced palliative effect on rheumatoid joints, as also did Kurtz and others.[226]

The only metabolic study of vitamin B in rheumatoid arthritis is that of Bayles, Palmer and others[31] who measured the excretion of various vitamin B components in forty cases. No significant difference was found between the excretion of thiamine, riboflavine or nicotinic acid in these patients as compared with a group of non-rheumatic controls.

Thus there is no significant evidence to date to connect avitaminosis B with the aetiology of rheumatoid arthritis.

Vitamin C. Many workers have tried to prove a relationship between vitamin C deficiency and the course and progress of rheumatoid arthritis. Rinehart and his co-workers reported in 1934 that a form of arthritis developed in scorbutic guinea pigs, with features resembling rheumatoid arthritis, and later, as a result of estimating blood ascorbic acid levels in rheumatoid arthritis, concluded that vitamin C deficiency is an important factor in the aetiology of the disease.[324,325,326] The finding of low vitamin C levels in a large proportion of cases of rheumatoid arthritis has been substantiated, although interpretations of the significance of this finding vary considerably. Sherwood[369,370] thought it indicated some abnormality of ascorbic acid metabolism, rather than a heightened demand for the vitamin. Hall, Darling and Taylor[163] in confirming the low blood levels concluded that, as some of their patients had no increased urinary excretion of ascorbic acid after oral saturation, the requirements for vitamin C are greater than normal in rheumatoid arthritis. Secher[357] found that patients with rheumatoid arthritis generally had no ascorbic acid in the blood, and also had decreased sugar tolerance curves which could be restored to normal by restoring the blood ascorbic acid levels, but does not discuss the significance of his observations. Freyberg[131] agreed that the majority of rheumatoid arthritics have low, almost scorbutic, blood vitamin C levels, although in some patients the level is always normal. He found that in general the blood ascorbic acid level is independent of the severity of the illness, is normal in the earliest stages and lowest in debilitated and undernourished patients, similar evidence of ascorbic acid deficiency occurring in a control group of patients in the same hospital with other, non-rheumatic chronic diseases. Because of these findings Freyberg considers vitamin C deficiency unrelated to the cause of rheumatoid arthritis.

From the facts available it would seem that vitamin C deficiency is a consequence of, rather than a causal factor in, the development of rheumatoid arthritis. The metabolic requirements of ascorbic acid for connective tissue formation are discussed in the section on the connective tissues.

Vitamin D. Although admitting doubt as to the justification for assuming arthritis in any form to be a deficiency of vitamin D, Dreyer and Reed[102] found marked subjective and objective clinical improvement to result from the administration of large doses of vitamin D and calciferol in twenty-four cases of rheumatoid arthritis, of whom only two failed to show benefit. Since then numerous publications on the effects of high-dosage vitamin D treatment have appeared, and claims for clinical improvement varying from 20 to 100 per cent of cases treated have been made. There is no sound basis for this treatment as there is no evidence of any primary disorder of calcium, phosphate or vitamin D metabolism in this disease, although patients with rheumatoid arthritis who have joint decalcification may present a slight but definite negative balance for calcium, corresponding to the radiographic degree of decalcification.[338] Freyberg,[131] in a long-term study of the effects of vitamin D treatment, found that any benefit attributable to therapy was infrequent and slight, and usually more subjective than objective, and thought any possible therapeutic value was outweighed by its toxicity and expense. Slocumb[376] came to similar conclusions, although Traeger[405] is more enthusiastic. Synder et al.[378] and Wagner[415] found the treatment of only dubious value. Even those writers who find this treatment to be of value fail to find any aetiologic rationale for its use.

Vitamin K. Rawls[315] states that he found hypoprothrombinaemia to be present in 50 per cent of patients with rheumatoid arthritis as well as in some patients with gout, and that administration of vitamin K restored the prothrombin levels of these patients to normal. The significance of these findings is not dis-

cussed, but they may be due to the depressive action of salicylates on prothrombin formation and therefore a result of medication.

ENDOCRINE DYSFUNCTION

Thyroid. Dysthyroidism in rheumatoid arthritis has been invoked by many workers, some claiming to find evidence of hyperthyroidism and some evidence of decreased thyroid function in cases of rheumatoid arthritis.[104,161] Others state that thyroid function cannot be correlated with this disease. Rawls et al.[316] noted no constant thyroid abnormality in 141 cases of rheumatoid arthritis; basal metabolic rates varied with the activity of the disease, being increased in the early and active cases, and subnormal in the chronic stages. An elevated basal metabolism rate in a patient with active arthritis becomes normal when the disease remits. Both thyrotoxicosis and myxoedema can coexist with rheumatoid arthritis, and temporary B.M.R. elevations, not in themselves indicative of hyperthyroidism, are a manifestation of the disease process. Plasma cholesterol levels were investigated in arthritics by Hartung and Bruger[170] who found a tendency to hypocholesterolaemia in rheumatoid arthritics and hypercholesterolaemia in osteoarthritics, both groups having a normal ratio of free to ester cholesterol. In a more detailed study of cholesterol metabolism, Granirer[148] found that plasma cholesterol levels tend to fluctuate in both types of arthritis, but the urinary excretion of cholesterol was normal in all cases. There was no correlation between plasma cholesterol, erythrocyte sedimentation rate and urinary cholesterol excretion. Wolfson and others[43] measured the uptake of radioactive iodine (I-131) and serum protein-bound iodine levels, indices more directly related to thyroid function than are the B.M.R. and serum cholesterol, in a series of rheumatoid patients, and found levels indicating the existence of significant hypothyroidism in about half of these patients. B.M.R. readings, total serum cholesterol and the ratio of free to ester cholesterol levels were within the range of normal in these subjects, indicating that a "masked, normometabolic hypothyroidism appears to be frequent in untreated rheumatoid arthritis." These workers could not relate the observed thyroid hypofunction to the state of disease activity, to malnutrition, to prior treatment with gold or to a "larval form of corticogenic hypothyroidism." However, knowledge of the variations of I-131 uptake and serum P.B.I. estimations in comparable chronic diseases is too limited to permit the authors to conclude that this masked hypothyroidism is a specific manifestation of rheumatoid arthritis.

It may be stated that there is still no conclusive evidence to incriminate thyroid dysfunction of either type as a factor in the genesis of rheumatoid arthritis.

Parathyroids. Because of the known effects of parathyroid hormone on bone and mineral metabolism, Helfet[175] believes that parathyroid dysfunction may bear a causal relationship to rheumatoid arthritis, a condition he terms "secondary hyperparathyroidism." In two cases of rheumatoid arthritis he noted advanced osteoporosis, "bone changes not dissimilar to fibrocystic disease," and the passage of a calcium phosphate stone, and quotes the reports of four authors on the same subject. He admits, however, that there is little biochemical evidence in favour of this theory. Periarticular bone cysts do occur as a manifestation of arthritis; but, nevertheless, although the rationale of the procedure is flimsy at best, parathyroidectomy has occasionally been performed as a therapeutic measure in cases of rheumatoid arthritis for twenty-five years, without any beneficial results.[240]

Pituitary. Histologic and histochemical studies on the pituitary have led Pearse[292,293] to postulate an affinity between rheumatoid arthritis and conditions of adrenal dysfunction. This worker has described specific changes affecting the mucoid cells (basophils and cyanophils) of the hypophysis in cases of rheumatoid arthritis. They consist, first, of the depletion and disappearance of the mucoprotein granules of these cells and their replacement by simple protein material, the so-called "Crooke-Russell" cells characteristically seen in Addison's disease. Secondly, the presence of a new type of cell, the "polar bigranulate cell," is described, occurring both diffusely and in groups or "adenomata." One-half of the cytoplasm of this cell is filled with beta granules and the other with simple protein granules similar to those in the Crooke-Russell cell. Apart from rheumatoid arthritis, polar bigranulate cells were not found in significant numbers in normal subjects or in other disease states. Pearse associates these two cellular changes with adrenal dysfunction, although he cannot exclude the possible responsibility of

other endocrines. This important observation has not yet been confirmed by others.

Functionally, both lobes of the pituitary appear to be normal in rheumatoid arthritis as far as can be judged by present methods of investigation. The response to adrenalin is unimpaired[404] and the urinary output of follicle-stimulating hormone is normal.[190]

Ovaries. There is no evidence that deficiency of oestrogens is involved in the pathogenesis of rheumatoid arthritis other than that this disease in women frequently occurs at the time of the menopause, and that postmenopausal women are subject to degenerative arthritis, "rheumatic" pains and arthralgias generally in association with other climacteric symptoms.[159,160] Villous or climacteric arthritis is said to be a form of arthritis of women at the menopause involving principally the knees, and while it has never been accepted generally as an entity, the claim is that it is neither atrophic nor hypertrophic arthritis.[396] The rheumatic and other menopausal symptoms in such cases frequently respond to oestrogens. Nevertheless the use of oestrogens in all cases of rheumatoid arthritis has its advocates.[272] Stone[397] believes that some cases of rheumatoid arthritis in the female are due to neuroendocrine disturbances in which pituitary and gonadal dysfunction and vitamin E deficiency all play a part, and claims great improvement from treatment with vitamins E and B and stilboestrol. Most of the reports of oestrogen therapy in rheumatoid arthritis lack rationale and adequate controls and beneficial effects of therapy are limited to menopausal women with arthritis. That the ameliorative effects of pregnancy on rheumatoid arthritis are not due to the associated increased levels of sex hormones at this time is emphasized by Hench.[176,177]

Recent evidence suggesting a possible abnormality of steroid metabolism in rheumatoid arthritis is the observation of Sommerville and others[384] that there is an abnormally high urinary excretion of pregnanediol when progesterone is administered to rheumatoid patients. On this basis it has been tentatively suggested that rheumatoid arthritis is associated with an abnormality of steroid metabolism peripherally in the tissues rather than a deficiency of endogenous steroid production. Corticotrophin does not alter the pregnanediol excretion after administered progesterone, and this has been supposed to indicate that the abnormality is a manifestation of the underlying disease process rather than a secondary effect of tissue inflammation. Since enzyme systems involved in the reduction of progesterone are probably similar to those involved in corresponding groups in adrenocortical hormones, a similar abnormality of adrenocortical hormonal metabolism may exist.[253] The rationale for the use of progesterone in the treatment of rheumatoid arthritis is based on the higher incidence of the disease in women, and especially in climacteric women; an alleged tendency of the disease to exacerbate at menstrual periods when progesterone levels are low; and the ameliorative effects of pregnancy on the disease. However, it has proved therapeutically very disappointing[2,214,215,283,412] as also has the use of a related steroid, Δ-5-pregnenolone.

Testes. Testosterone alone and combined with other steroid has been used of recent years in the treatment of rheumatoid arthritis, and although it may be useful in some cases for its protein anabolic effects it does not influence the course of the disease and there are no grounds for believing that testicular androgens are in any way concerned in the causation of the disease.[194,250]

Adrenal Cortex. The demonstration of the effects of costisone and corticotrophin in rheumatoid arthritis focussed attention on the possible role of the adrenal cortex in its pathogenesis. It soon became clear that the action of the hormones is not due to deficient output of cortisone by the adrenal; hormone therapy is not replacement therapy in this disease. The adrenals are anatomically normal in rheumatoid arthritis.[381] Functionally, the over-all production by the adrenal of neutral 17-ketosteroids and reducing steroids is widely reported as being unimpaired,[90,96,128,179,435] although Bauer, Clark and Dienes[26] and Howard et al.[190] report subnormal or low normal excretions of these steroid groups in rheumatoid arthritis. Electrolyte balance is maintained,[190,253] and the adrenocortical response to ACTH and adrenalin is normal. The association of rheumatoid arthritis and clinical adrenocortical insufficiency (Addison's disease) is very rare and most probably fortuitous. When it does occur, however, both the arthritis and the adrenal insufficiency respond to cortisone in the usual way.[58,111]

Marrian[253] points out that although there is no evidence of abnormality in the urinary excretion of endogenous adrenocortical steroids, an abnormality in the metabolism or secretion of the C_{21} group of hormones would not necessarily result in any alteration in the total excretion of

17-ketosteroids. At the present time the use of newer techniques for the fractionation and separation of the urinary steroids seems to be yielding evidence that an abnormality of steroid excretion might well be present in rheumatoid arthritis. Kellie and Wade[211] have recently claimed that fractionation studies of the 17-ketosteroids in the urine of rheumatoid patients show a reduced excretion of both "ketonic" and "non-ketonic" material, with a markedly decreased proportion of ketonic alcohols excreted as androsterone, and an increased proportion as aetiocholanolone. In these patients corticotrophin administration caused a marked increase in all the fractions excreted, and a reversion of the androsterone-aetiocholanolone ratio toward normal. Cortisone did not have this effect. Norymberski, Stubbs and West[282] have also found a change in the pattern of urinary steroid excretion in rheumatoid subjects as compared with controls. They describe a method for determining a structurally well defined group of urinary corticosteroids designated 17-ketogenic steroids. They found that in rheumatoids the average daily excretion of these steroids was 40 per cent below normal values. When cortisone was given by mouth, urinary excretion was directly related to intake. ACTH caused an increase excretion of these steroids. The authors believe that the daily output of 17-ketogenic steroids reflects mainly the adrenal secretion of 17-hydroxycorticosterone (compound F), which Nelson and Samuels[275] have shown to be the principal cortical steroid secreted into the blood; if this is so, estimation of urinary 17-ketogenic steroids is therefore an important measurement of adrenal activity. Dobriner[99] reports that a steroid, 17-hydroxypregnenolone, occurs in the urine of rheumatoid arthritics. This compound is not a 17-ketosteroid but is said not to be found in normal urine.

Thus evidence is beginning to accumulate that an abnormality of steroid metabolism may be present in rheumatoid arthritis but whether this is causally related to the disease process, or a result of it, is at present impossible to say.

METABOLIC DISORDERS

Sulphur Metabolism. Rheumatism in all its forms, including rheumatoid arthritis, has for centuries been treated with sulphur given by mouth as a colloidal suspension or in the form of natural spa waters, and even intravenously, on a purely empiric basis. There is a large literature on the clinical uses of sulphur in arthritis, some claiming it to be of great therapeutic value[12,366,399,427] while others deny that it has any value.[185,403] The literature on colloidal sulphur in the treatment of arthritis is reviewed by the A.M.A. Council on Pharmacy and Chemistry.[6] There have been few accurate studies on sulphur metabolism in arthritis but what there are are inconclusive in demonstrating any abnormality. Sullivan and Hess[399] claimed to find a lowered cystine content of the fingernails in 103 arthritics compared with twenty-six normal subjects but the statistical validity of their figures is doubtful. Goldthwait, Painter and Osgood[145] found that two patients with atrophic arthritis eliminated more sulphur than they ingested. Senturia[367] estimated the urinary sulphur of healthy individuals and of patients with osteoarthritis and rheumatoid arthritis, and concluded that the sulphur excretion and sulphur partition in the urine of the two groups of arthritics showed no appreciable deviation from the normal. Wheeldon and Bosher[428] found normal concentrations of glutathione, inorganic sulphate, total sulphur and total sulphate in the blood, and of sulphate in the urine, of seventy-four cases of osteoarthritis and rheumatoid arthritis, but nevertheless found that many of these patients improved clinically on sulphur therapy. Freyberg, Block and Fromer[132] in a careful study of four cases of rheumatoid arthritis and controls found no evidence of sulphur deficiency, or abnormality of sulphur metabolism, to exist in arthritis, and no benefit to result from sulphur medication. The distribution of urinary sulphur was the same in all groups except that the rheumatoid arthritis patients excreted an insignificantly higher percentage in conjugated form. The metabolism of colloidal sulphur administered orally and parenterally was the same in both groups. Daily analyses showed no indoluria. The cystine content of the fingernails was normal in most cases and unexpectedly low in a few, but was not increased in any by the administration of large amounts of colloidal sulphur or sulphur-containing salts. On the evidence of this study the authors conclude that there is no biochemical or metabolic indication of, need for, or benefit from sulphur medication in arthritis.

Disordered Liver Function. It has long been suspected that there might be some derangement of hepatic metabolism in rheumatoid arthritis, chiefly because of the finding of abnormalities in certain biochemical tests which are also fre-

quently altered in liver disease, but no primary alteration of hepatic function has been established.

A disorder of carbohydrate tolerance was first observed by Pemberton and Foster[295] in rheumatoid arthritics given oral glucose, the blood sugar curve showing a slow return to the fasting level. Similar findings after intravenous glucose were demonstrated by Flynn and Irish[124] who considered them an indication of disordered hepatic control of carbohydrate. Andrews and Muether[7] believe the glycogenolytic capacity of the liver is decreased in rheumatoid arthritis, on the basis of finding high arterial sugar tolerance curves compared with normal arteriovenous differences in simultaneous venous curves.

The abnormal sugar tolerance in rheumatoid arthritis has never been satisfactorily explained but there is no *prima facie* evidence that it is due to hepatic dysfunction.

The ability of the liver to synthesize hippurate in rheumatoid arthritis has been investigated, and Rawls et al.[318] found a deficiency of hippurate synthesis in twenty of fifty subjects, together with elevated serum icteric indices and hypoalbuminaemia. More than half of their patients also had disordered biliary excretion of azorubin S given intraduodenally.[317] Hepburn and others[182] and Lemon and others,[233] on the other hand, found hippurate synthesis to be normal in the cases they studied. Hepatic efficiency measured by tolerance to intravenous bromsulphalein was found by Robinson[333] to be unimpaired in twenty-one cases of rheumatoid arthritis.

The capacity of patients with rheumatoid arthritis to acetylate *p*-amino-benzoic acid and sulphadiazine was found by Kuhl, Gershberg and Ralli[255] to be unimpaired and uninfluenced by oral calcium pantothenate, but it is thought that this may not necessarily exclude gross hepatic disease.[138]

Lövgren[56,248] believes the cause of rheumatoid arthritis to be a reduction in the power to convert carbohydrate, due in turn to functional disturbances in the adrenal cortex or hypophysis. In 100 cases of the disease he found subnormal blood citric acid levels with elevated blood pyruvate levels, raised serum globulins and normal A/G ratios. These biochemical abnormalities were corrected by the administration of adenosine triphosphate (ATP), given to stimulate carbohydrate conversion, and were accompanied by marked clinical improvement in two-thirds of the cases. This worker believes the fault in carbohydrate conversion in rheumatoid arthritis to lie in the liver, and believes this is supported by his observation of non-specific anatomic changes in the livers of 61 per cent of his cases. He believes the effects of cortisone in rheumatoid arthritis may be due to its influence on ATP enzyme groups. Other workers have failed to find any benefit from the administration of ATP in rheumatoid arthritis.[143,425]

The main evidence for the assumption of disordered liver function in rheumatoid arthritis has been the finding of abnormalities of the plasma proteins and of non-specific "liver function" tests related to abnormal plasma globulins. The tests which are frequently positive in rheumatoid arthritis are the colloidal gold, cephalin-cholesterol flocculation and thymol turbidity reactions,[11,57,127] the colloidal gold reaction being the most frequently abnormal. It has been generally found that the plasma proteins are altered in rheumatoid arthritis in the direction of low or low-normal albumin, and elevated globulin levels.[11,271,401] The abnormal flocculation tests mentioned are always associated with hyperglobulinaemia. The major increase in the globulin is in the euglobulin fraction.[89] Electrophoretically, both alpha and gamma globulins are increased, the changes in all the protein fractions returning to normal when the disease remits.[100,300] A similar pattern is to be found in acute rheumatic fever.[101] The increased alpha globulin can be correlated with an increase in "C-reactive" protein, which is contained in the α_1 globulin fraction.[299]

It is impossible to interpret the varied and often contradictory data concerning liver function in rheumatoid arthritis in terms of aetiology, partly because of the doubtful significance of most of the tests used and also because of the different hepatic functions assessed. Anatomic studies of the liver in rheumatoid arthritis fail to demonstrate any characteristic lesion.[20,271] It is very doubtful whether the abnormalities of the plasma proteins found by chemical and electrophoretic studies, or indirectly by the presence of abnormal flocculation tests, reflect disordered hepatic function. There is, too, no definitive evidence relating such disorders of carbohydrate metabolism as have been found to an hepatic aetiology.

It may be concluded that there is as yet no evidence for an aetiologic relationship between a

primary disorder of liver function and the development of rheumatoid arthritis.

THE CONCEPT OF THE COLLAGEN DISEASES

The multifocal pathologic involvement of mesenchymal connective tissues throughout the body in rheumatoid arthritis can best be explained as a non-specific disturbance characterized anatomically by systemic alterations in the connective tissues, especially the extracellular elements. Microscopically, this alteration takes the form of "fibrinoid" degeneration, swelling and sclerosis of collagen fibrils and an increase of metachromatic ground substance.[220] Klinge[225] in 1933 first drew attention to the systemic character of the connective tissue lesions in rheumatic fever and their similarity to the tissue changes in the hyperergic state. Subsequently Klemperer designated disseminated lupus erythematosus and diffuse scleroderma as systemic connective tissue diseases.[221,222] The term "collagen-vascular diseases" has been used to emphasize the systemic nature and the similarity of the connective tissue lesions of a group of diseases which includes also rheumatoid arthritis, rheumatic fever, periarteritis nodosa and dermatomyositis. In these diseases changes occur not only in the collagen fibres as such but also in the interstitial connective tissue as a whole, and evidence that the observed changes in the collagen fibres constitute the primary lesion is as yet almost wholly presumptive. For these reasons "connective tissue diseases" is a nosologically more appropriate designation than is "collagen diseases."

Many clinical and laboratory manifestations are common to the disorders in this group, and cases are on record of illnesses combining the clinical, laboratory and pathologic features of two or more of the disorders. Such transitional cases can cause much diagnostic and pathologic difficulty and have been called "diffuse collagen disease."[51,200,206,207,219,222,309,437] They serve to emphasize the probable pathogenetic unity of the syndromes comprised in the group.

Physiology of Connective Tissues. The application of the newer techniques of histochemistry and electron microscopy, the use of specific proteolytic enzymes and x-ray diffraction studies on thin sections of tissue have recently illuminated the study of the connective tissues in healthy and morbid states but knowledge of this subject is still fragmentary. However, a brief résumé of current knowledge of connective tissue physiology is essential if data concerning its systemic alterations are to be appreciated.

Connective tissue has supportive and nutritional functions and consists of the scleroprotein fibres collagen, reticulin and elastin lying in a matrix of amorphous mucoid ground substance rich in mucopolysaccharides. The nutrition of most cells occurs across this intercellular matrix which permits diffusion of nutritive materials between capillaries and cells. The precise composition of ground substance is unknown, apart from its mucopolysaccharide content at various sites. Both it and the supporting fibres of connective tissue are probably formed by fibroblasts; at any rate the fibroblast is essential for collagen formation.[389,390] Electron microscope studies appear to indicate that young collagen fibres are actually spun off the surface of the fibroblast.[305]

Conventional histologic staining methods for collagen yield little or no information concerning its constitution and are non-specific.[155] Native collagen fibres are digested by pepsin in acid solution and by clostridial collagenases but are stable to trypsin, cathepsins and other proteolytic enzymes.[277,373,374] Thermally contracted collagen is said to be dissolved by elastase.[22] Collagen is unique among the body proteins in containing 13–14 per cent of hydroxyproline,[37,42] the only other site of this amino acid being elastin which has less than 2 per cent.[276] Other important constituents of collagen are the amino acids glycine and proline, and possibly a little mucopolysaccharide,[231] although some workers doubt this.[351]

The use of the electron microscope has revealed morphologic details of normal and abnormal connective tissue. The structure of collagen is described as a bundle of fibrils embedded in an amorphous matrix of acid polysaccharide and protein. Normal collagen fibres are about 1,000 Å in width and exhibit a constant pattern of cross-striation with an average periodicity of 640 Å, this being true of all natural collagens.[157,349] This periodicity can be used to differentiate normal from abnormal collagens, and Porter[305] has made the important observation that under abnormal conditions of metabolism collagen fibres are formed which are structurally abnormal. Also Highberger, Gross and Schmitt[183] have produced evidence that bovine plasma mucoprotein and a purified acid glycoprotein from human plasma, but not the acid polysaccharides hyaluronate or heparin, may play a part in the formation of both normal

and abnormal collagens. Jackson[195] believes the mucopolysaccharides, especially chondroitin sulphate, are of importance in maintaining the stability of collagenous fibres and indicates the possibility that some disorder of the protein-carbohydrate complex may be concerned in the pathogenesis of the connective tissue diseases.

The interfibrillar ground substance is composed of carbohydrate-protein complexes, the chemistry of which is reviewed by Meyer[262] and Schubert.[351] Six mucopolysaccharides have been isolated from mesenchymal tissues in which they occur as salts rather than as free acids. The three important ones are hyaluronate, chondroitin sulphate and heparin. All are composed principally of a hexosamine and hexuronic acid (glucuronic acid) in equimolecular proportions. The hexosamine is in most cases N-acetyl glucosamine but in chondroitin sulphate it is galactosamine. Four of the known tissue mucopolysaccharides contain also an ester sulphate group. Mucopolysaccharides can be demonstrated in the tissues by histochemical means using the periodic acid-fuchsin reagent of Hotchkiss[189] which stains them red to purple. They can also be demonstrated by the fact that in tissue sections they stain metachromatically with azo dyes such as toluidine blue. The acid mucopolysaccharides are hydrolysable by the enzyme hyaluronidase. Hyaluronate and chondroitin sulphate, the principal polysaccharides of connective tissues, are both hydrolysed by testicular hyaluronidase, but pneumococcal hyaluronidase hydrolyses only hyaluronate. It is not yet known whether hyaluronidases from different sources are the same or different enzymes.[263]

Little is known of the metabolism of the connective tissues but it is evident that ascorbic acid is necessary for the formation of interfibrillar ground substance and of the connective tissue fibres,[137,297] although not in itself part of the chondroitin sulphate or collagen molecule.[49] In scorbutic guinea pigs the finest connective tissue fibres disappear rapidly;[433] and since ascorbic acid is not necessary for the maintenance of pre-formed collagen.[112,329,330,331] the decrease is probably due to deficient formation of new fibres. Wolbach believes the defect in scurvy lies in the extracellular conversion of a collagen precursor into collagen.[432] Robertson and Schwartz,[332] from analyses of experimentally produced collagen in normal and scorbutic guinea pigs, suggest that the function of ascorbic acid in collagen formation may be related either to the synthesis of hydroxyproline or to its introduction into the collagen macromolecule. But whatever the precise role of ascorbic acid in connective tissue formation may be, the end results of its deficiency are clear, namely a failure in the supply of collagen for maintenance of connective tissue fibres and ground substance.

Chondroitin sulphate is the chief mucopolysaccharide of cartilage. Hyaluronate is present in large amounts in subcutaneous tissue but there is little or none in loose connective tissue and it is not found in the blood.[105] With increasing age there appears to be increased production of chondroitin sulphate at the expense of hyaluronate. So far, unlike the chondroitin sulphate of cartilage, that of connective tissue has not been obtained in undegraded form.[263] There is evidence that in normal human articular cartilage the proportion of chondroitin sulphate relative to the amount of fibrous collagen bears an important relationship to function, a higher proportion of the polysaccharide being associated with greater resilience of the cartilage in the weight-bearing areas.[256] In this respect chondroitin sulphate appears to have plasticizing properties. In osteoarthritis there is a progressive loss of mucopolysaccharide ground substance from articular cartilage relative to its collagen content,[257] a change characteristic of the aging process.[241] The chemical composition of articular cartilage in rheumatoid arthritis has not yet been studied.

Synovial fluid contains hyaluronate[264] in the greatest concentration in the body, and it is this that is responsible for its characteristically high viscosity. This property is due to the large size of the hyaluronate molecule (of molecular weight at least 500,000) and its high degree of polymerisation.[154,263] Chondroitin sulphate also has a high molecular weight and a long-chain molecule and is closely related to hyaluronate chemically, but nevertheless has a viscosity little greater than that of water.[351] The hyaluronate in synovial fluid forms salts with proteins which precipitate at acid reaction and synovial mucin is demonstrated by this means. Actually, the viscosity of synovial fluid is greater than that of a solution of hyaluronate of equivalent concentration, and Ogston and Stanier[284] have shown that this is because, in the fluid, the hyaluronate is not free but is bound to protein as a complex which is broken when the hyaluronate is isolated. Studies of the mechanics of synovial

fluid strongly suggest that the major function of hyaluronate is its contribution to the lubricant properties of the joint.[285,286,337]

Alterations of the Connective Tissues in Disease. Synovial fluid is essentially a dialysate of blood plasma[29] modified by the differential permeability of the synovial membrane to individual blood protein fractions[336] and by the addition of hyaluronate in the proportion of 0.3–0.8 per cent, secreted by modified connective tissue cells in the synovium, probably mast cells.[13] In traumatic synovitis and in osteoarthritis the volume of synovial fluid may be greatly increased but the mucin content, relative viscosity and glucosamine concentration remain normal, indicating no degradation or alteration of the polysaccharide.[323] Rheumatoid arthritis is characterized by an excess of synovial fluid containing increased total amounts of hyaluronate, nevertheless the fluid has a characteristically low viscosity, and mucin clot formation on acidification is impaired.[314] This apparent degradation of synovial mucin is not due to hyaluronidase activity, as hyaluronidase has never been detected in synovial fluid or synovial tissues, and enzymatic activity could not account for the increase in total hyaluronate. In addition, free hexosamine is never found in such fluids.[323] Ragan and Meyer believe that in rheumatoid arthritis there is an increased production of incompletely polymerised hyaluronate, and that the fault lies in the connective tissue cells which are unable to synthesize a high-polymer mucopolysaccharide. Hyaluronate does not appear in the blood of subjects with rheumatoid arthritis or other connective tissue diseases.[438]

At present there is little knowledge concerning chemical changes in diseased connective tissue components *in vivo*. In serous inflammation of any type the basic change in the ground substance is an increase of metachromatic polysaccharides, as well as the accumulation of protein material. The source of the polysaccharides is unknown but they may be secreted by the mast cells, which normally store the non-acetylated mucopolysaccharide, heparin. When the inflammatory agent is mild or transient, these intercellular changes are reversible but as the lesion becomes chronic the oedematous, metachromatic tissue is converted into an amorphous collagen-lipoid complex of hyaline.[327]

Electron microscopic studies of collagen in the collagen-vascular group of diseases have so far yielded surprisingly little information. Kellgren and others,[210] in a classic x-ray diffraction, histologic and electron microscopic study of the same sections of rheumatoid nodules, found only apparently normal collagen fibrils and structureless "fibrinoid debris." Gross[156] had the same experience with rheumatoid nodules and synovium, and with skin from disseminated lupus and scleroderma cases. Gale[133] found no significant change in structural characteristics or periodicity of the collagen fibrils in the lesions of rheumatoid arthritis, rheumatic fever and disseminated lupus. However, Wolpers[436] described collagen fibrils without cross-striation in the necrotic portions of old rheumatic nodules. In the non-necrotic areas he found only normally striated fibres in tissues showing fibrinoid change, and concluded that the primary change was in the ground substance. Recently, Rich, Voisin and Bang[322] have described important ultramicroscopic changes in the collagen at the local reaction site of the Arthus phenomenon in the anaphylactically sensitised animal. A proportion of the collagen fibrils showed loss of cross-striation, swelling, irregularities of contour and density, and fragmentation. The appearances corresponded with those seen with the light microscope in this lesion, and with similar lesions seen in diseases of the collagen-vascular group. This observation is of importance in indicating that a primary alteration of the elementary collagen fibrils themselves can occur in the diseased state, in addition to changes in the ground substance in and about the fibre bundles, but it has yet to be confirmed. It also provides some evidence for the possibility that some at least of the diseases in this group may be immunologically determined.

Little is known of the metabolism of connective tissues in health or in the rheumatic diseases, although judging by the negligible oxygen consumption of adult connective tissue its metabolic activity in health is probably low.[50] Kellgren[208] quotes the work of Slack and others who measured the uptake of C^{14}-labelled glycine by the collagen of various sites in rats of different ages. These experiments suggest that, once laid down during growth, collagen becomes metabolically relatively inert. Kellgren therefore believes that rapidly developing collagen disorders are unlikely to be the result of faulty collagen synthesis. Stetten[394] has shown that the uptake of N^{15}-labelled dietary hydroxyproline by the body proteins in rats and mice is less than 0.1 per cent.

Other chemical studies seem to confirm the belief that collagen is metabolically almost inert. Neither the amount nor the concentration of collagen is decreased in scorbutic guinea pigs[112, 329,330] even though ascorbic acid is required for its formation.[433] This stability of collagen in the absence of an essential growth factor seems to indicate that the molecule once laid down does not undergo extensive degeneration and resynthesis. Robertson[331] found from feeding experiments with isotopically-labelled glycine in normal and scorbutic guinea pigs that there was a small turnover of radioactive nitrogen in collagen without any appreciable breakdown of the macromolecule, and this was uninfluenced by ascorbic acid, even in scorbutic animals.

In patients with rheumatoid arthritis de Vries and Alexander[413] found low blood levels of glycine and low oral glycine tolerance curves, suggestive of increased tissue utilization or increased destruction of this amino acid. Lemon, Chasen and Looney,[233] claim to have demonstrated a deficiency of available extrahepatic glycine for hippurate synthesis in patients with rheumatoid arthritis, rheumatic fever and disseminated lupus, not present in other diseases and unaccompanied by deficiency of other amino acids. As glycine accounts for nearly one-third of the total amino acid residue of collagen and elastin, failure of its supply might lead, the authors believe, to impaired collagen production or abnormal collagen formation. These observations have not been confirmed and no analysis of the amino acid content of diseased collagen has been made. Ziff and Dresner[439] found no increased urinary excretion of hydroxyproline in subjects with a variety of connective tissue diseases as compared to healthy subjects and to subjects with non-rheumatic diseases. This would suggest that at least no major breakdown of collagen in these disorders is detectable, although it does not of course imply that structural changes in the collagen have not taken place.

Fibrinoid. As previously mentioned, the collagen group of diseases have a common lesion of the interstitial connective tissue, especially its extracellular component.[218,219] This begins histologically as a swelling of the interfibrillar ground substance and of the fibres themselves, and then fibres and ground substance become merged into a highly refractile, homogeneous, relatively acellular, eosinophilic material with the staining properties of fibrin, and containing many reticulin fibres. To this material Neumann[278] first applied the term "fibrinoid" in view of its tinctorial affinity to fibrin.

Fibrinoid is found in the connective tissue not only of the group of diffuse collagen diseases[218, 219,221,222] including rheumatoid arthritis and rheumatic fever[33,223] but also in the base of peptic ulcers, in the placenta,[4,5] in the connective tissue of the heart valves in terminal endocarditis[3] and in hyperergic reactions.[95,321] It is also said to be caused by the administration of large amounts of DCA[360] and to be present in the renal lesions of diabetes.[224] Its presence in the renal arterioles in malignant hypertension is well known. Thus although fibrinoid is a constant feature of the collagen group of diseases, it is by no means a specific lesion, and seems to be a connective tissue response to perhaps many different injuries. With the limited methods at present available fibrinoid appears to be identical in all instances, although its presence in a variety of disease states cannot be assumed to imply a common aetiology.[219,221] Morphologically, foci of fibrinoid in various sites generally permit pathologic differentiation of the collagen diseases. It would seem that a pathognomonic modification of the fundamental connective tissue lesion in each of the collagen diseases gives it in each a distinct localization and a specific type of cellular reaction.

The fundamental nature of fibrinoid is still unknown, although there is clearly some profound physiochemical alteration of the interfibrillar ground substance and perhaps of the scleroprotein fibres also. Intense positive staining with the periodic acid-Schiff reagent indicates a change in the mucopolysaccharide component, and chemical analysis shows it to be quantitatively increased.[82] The belief of Clark and others[69] that the fibrinoid of atheroma represents compressed and hyalinized blood elements and the remnants of organising thrombus is not generally held and is not substantiated by current methods of investigation.[83,142] Purely from the histologic appearances of fibrinoid, Klinge[223] and Schlossmann[348] concluded that it represented degenerated collagen fibres. From studies of the digestive action of various enzymes, including trypsin and a crude clostridial collagenase, and from histochemical studies on the fibrinoid of rheumatic fever nodules, Glynn and Loewi[142] reached the following conclusions: fibrinoid differs from fibrin in its fibrillar structure and by its resistance to trypsin. It

differs from collagen in its argyrophilia and strongly positive reaction for polysaccharide by the PAS technique. It resembles collagen in its digestion by collagenase and by trypsin after treatment with heat or urea. The loss of the strongly positive PAS reaction after treatment with potassium salts indicates the presence of large amounts of polysaccharide. They conclude: "Fibrinoid change is brought about by the infiltration of collagen with a polysaccharide-rich material, possibly a glucoprotein." Klemperer[219,222] suggests, from study of the lesion in lupus erythematosus and scleroderma, that as well as changes in the collagen fibres the possibility of an imperfect formation of ground substance should be considered; Altschuler and Angevine,[4,5] from their histochemical studies, believe that only the ground substance is involved in the formation of fibrinoid, the essential feature of which is the precipitation of the interfibrillar acid mucopolysaccharides by an alkaline protein formed in the necrotic tissue or produced by the causal agent. Kellgren and others[210] believe, on histochemical grounds, that fibrinoid may not be homogeneous but may represent alterations both in the collagenous and the polysaccharide components of connective tissue. By the simultaneous use of histochemical stains, x-ray diffraction diagrams and electron microscopy on the same sections of rheumatoid nodules, these workers have shown that the x-ray diffraction diagram and the ultramicroscopic structure of fibrinoid differs greatly from that of normal collagen, which exists side by side with it in the same section. Also the x-ray diagram of fibrinoid differs from that of fibrin. Further evidence against the collagenous constitution of fibrinoid is provided by Bien and Ziff[34] who found, by analyses of the collagen of rheumatoid nodules and synovial tissue for hydroxyproline by the method of Neuman and Logan,[276] that the content of this amino acid was similar to that found in collagen from other sources, the total hydroxyproline content of the nodules and synovial membrane being accounted for completely by the collagen and elastin fractions. Ziff et al.[440] also analysed fibrinoid, separated from rheumatoid nodules by treatment with either dilute alkali or trypsin digestion, for its hydroxyproline content by the highly sensitive chromatographic technique using isotopically labelled pipsyl chloride of Keston et al.[217] They found only traces of hydroxyproline comparable to the amounts found in extracts of normal skin. These workers concluded that the composition of fibrinoid differs from that of collagen and does not include collagen protein as such. They also found that, in contrast to the observations of Glynn and Loewi, fibrinoid was resistant to the action of a potent clostridial collagenase.[201] Chemical examination of rheumatic fever nodules by Consden, Glynn and Stanier[83] led them to the conclusion that there is little reason for supposing that such nodules contain substances not present in normal tissue.

It is generally agreed that the morphologic similarity of the fibrinoid change in the collagen group of disorders and other diseases does not provide evidence to indicate a unitarian aetiology between the various disorders in the group, or between this group and the hypersensitivity states in which it also occurs. Despite this and the lack of evidence that all fibrinoid material has the same composition, it is hopeful to assume that a knowledge of the physicochemical nature of this basic tissue change would throw some light on the pathogenesis of the disorders in which it occurs. But as the studies cited show, the subject is one of great complexity and there are as yet no definitive trends in the data so far provided. It would appear that, although some fibrin may be present it is not an important constituent; collagen is not present in any recognisable form, and mucopolysaccharides are present in quantitatively increased amounts, possibly in a depolymerised state. Kellgren[208] postulates that diffusion of peptide degradation products of collagen into the tissues may, by their toxic nature, excite the inflammatory features of rheumatoid arthritis. This he believes may take place in a widespread manner throughout the connective tissues, without the formation of an appreciable quantity of fibrinoid residue, and would explain also the generalised connective tissue atrophy and the osteoporosis, which cannot be accounted for on the basis of disuse or on the excessive tissue catabolism of tissue injury. The work of Lewis[236,237] on the production of inflammatory reactions by substances liberated from damaged tissue, and of Menkin[260] on the reproduction of the local and systemic features of inflammation by simple peptides from inflammatory states, would seem to lend indirect support to Kellgren's view that the inflammatory and toxic features of rheumatoid arthritis could result from a primary disintegration of collagen.

Differential Sheep Cell Agglutination Reaction. In 1948 Rose and others,[339] while performing complement fixation tests for rickettsial pox, noted that sera from patients with rheumatoid arthritis agglutinated sheep erythrocytes sensitised with rabbit antisheep cell amboceptor to a higher dilution than did non-rheumatic sera. This finding was soon confirmed and the test improved.[21,197,267] Kellgren[208] has reported the results of this test in nearly 2,000 individuals. While 47 per cent of patients with rheumatoid arthritis gave positive reactions they were rarely positive in other diseases with the exception of disseminated lupus erythematosus and dermatomyositis. Further, the incidence of positive reactions in rheumatoid arthritis was greatest in patients with subcutaneous nodules (80 per cent), and low in patients with psoriatic arthritis (7 per cent) in which nodules rarely if ever occur. It is also low in children with Still's disease.[355] Rose and his co-workers and others have related the higher incidence of positive reactions with the degree of activity of the disease in adults.[197,398] Pike et al.[303,304] observed that rheumatoid sera not only agglutinate sheep cells sensitised with the usual rabbit anti-sheep-cell serum, but also agglutinate sheep cells sensitised with rabbit anti-goat cell serum and with rabbit anti-guinea pig kidney serum. Sheep cells sensitised with serum from patients with infectious mononucleosis and normal persons are agglutinated to about the same degree as unsensitised cells. Adsorption of agglutinins for group A streptococci from rheumatoid serum does not affect the serum titre for sensitised sheep cells. The property of amplifying specific agglutination is present to a small extent in some human and animal sera, and the marked activity in rheumatoid sera may simply represent an increase of this normal property.

The test appears to have a high degree of specificity for rheumatoid arthritis and collagen diseases characterized histologically by the presence of fibrinoid, with the exception, as Kellgren points out, of rheumatic fever. The nature of the sheep cell agglutinating factor is not completely known. Rose demonstrated it to be in the globulin fraction of the serum and differentiated it from the haemolytic streptococcal agglutinating factor. The reaction is independent of heterophile antibody, which can be removed without affecting the titre against sensitised red cells.[414] To Hobson and Gorrill[184] the activity of the rheumatoid agglutinating factor against several combinations of red cells sensitised with antibody, but not against unsensitised cells, suggests a complement-like activity. They found a correlation between raised agglutinating titres in rheumatoid sera and increased lytic titres of the fourth fraction of complement, and tentatively suggest that it may be inferred that this fraction has an agglutinating action. This has yet to be confirmed.

Like the other agglutinating and precipitating factors in rheumatoid serum, the agglutinin for antibody-sensitised sheep red cells is a globulin which probably in some way alters the physicochemical equilibrium of the serum. It is most probably a direct manifestation of the rheumatoid process, as opposed to other, non-specific inflammatory phenomena, as it is uninfluenced by natural or hormone-induced remissions of the disease. Until this factor can be isolated and characterized its pathogenetic relationship to rheumatoid arthritis cannot be properly determined, but from its high degree of specificity for this disease, its observed relationship to the presence of fibrinoid, and its failure to be suppressed by steroid therapy when effective in suppressing other manifestations of the disease, it seems likely that it reflects in some way the fundamental pathogenetic disorder of rheumatoid arthritis.

HYPERSENSITIVITY AND RHEUMATOID ARTHRITIS

Allergy or acquired hypersensitivity of the tissues to some exogenous stimulant has often been considered as the possible cause of rheumatoid arthritis since it was first suggested by the work of Klinge in 1933. In the past many allergic hypotheses have been made on the basis of purely clinical observations. From the study of a group of mixed arthritides, Pottenger[306] considered chronic arthritis to be an allergic reaction to foods but his evidence was tenuous and he offered no clinical or laboratory findings to support this, other than the observation that a large proportion had "allergic manifestations" of one sort or another. Allergy to foodstuffs was also thought an important factor in rheumatoid arthritis by Vaughan[410] and Turnbull.[406] The former found 2.7 per cent of cases of "recurrent subacute arthritis" in 1,000 patients with allergic disorders, in all of whom the offending allergens were foodstuffs. The latter skin-tested arthritics for dietary allergens and stated that elimination of these, when found, produced a "high percentage of complete relief."

Allergy to bacteria or bacterial products was postulated by Levinthal.[235] On the basis of finding a higher proportion of positive agglutination reactions to haemolytic streptococci in the synovial fluids than in the sera of rheumatoids, he believed that antibodies were frequent in the tissue cells in this disease, and that a non-specific bacterial allergy was the likely cause. But the theory of bacterial allergy was not acceptable to Aschoff[15] who, from histologic studies of the lesions of rheumatoid arthritis concluded that "allergy plays no part . . . in rheumatoid diseases arising from specific or non-specific infections." Davidson's[87] concept is that in rheumatoid arthritis there is an abnormal immunologic response of the tissues to bacterial proteins. He pictured such allergens entering the circulation, coming in contact with fixed tissues in the joints, and provoking an allergic reaction "evidenced by an explosive discharge of histamine-like substances which produce dilatation and increased capillary permeability, and hence swelling of soft tissues, heat and pain." In other words, an anaphylactoid reaction.

The work of Rich and his colleagues supporting the theory of rheumatoid arthritis as a hypersensitivity disease has been reviewed by him in a Harvey Lecture.[321] Briefly, Rich emphasises the basic identity of the tissue lesions of disseminated lupus erythematosus, periarteritis nodosa, rheumatic fever and rheumatoid arthritis, serum sickness, anaphylactoid purpura and acute glomerulonephritis, and shows how histologically identical focal collagen and necrotizing vascular lesions can be produced in animals by injections of antigenically active proteins. He believes that an acquired anaphylactic type of hypersensitivity to a foreign antigen, bacterial or non-bacterial, protein or hapten, is the pathogenetic basis of all these conditions. He emphasises, however, that basic identity of lesions is not proof of identity of aetiology, but points out that in the diseases listed not only are the basic tissue disturbances those that are known to occur in anaphylactic reactions, but these diseases also exhibit in common a wide variety of manifestations which clinical, pathologic and experimental studies have shown to be effects that the anaphylactic state can produce. He also stresses that in the case of lesions in which hypersensitivity constitutes the actual *pathogenetic* mechanism of injury, the *aetiologic* agent may be quite different in different cases. As examples he cites as aetiologic agents in periarteritis nodosa such widely differing substances as foreign proteins, iodine[320] and sulphonamides, and discusses the possibility of such a relationship between the haemolytic streptococcus and rheumatic fever. He quotes experimental evidence which lends support to the view that, under varying conditions such as contact with bacterial products, components of the body tissues may become antigenic and incite the formation of tissue-specific antibodies. There is some evidence that in man some hypersensitivity reactions may be governed, in part at least, by hereditary predisposition, although the actual mechanisms governing differences in susceptibility to, and sites of action of, hypersensitivity reactions are still obscure. Hawn and Janeway[171] have confirmed the experimental production in rabbits, by intravenous injections of foreign serum, of necrotizing arteritis, acute nephritis and lesions in the joints and heart all closely resembling those found in various human collagen diseases. Their interpretation that the pathologic lesions in these experiments are due to an antigen-antibody reaction in affected tissues is supported by the results of the immunologic studies they present. Similar lesions can occur in homologous organ transplants, apparently due to the same type of hypersensitivity reaction.[95] More[268] notes the morphologic similarity between the mononuclear cellular reaction of the tissues in the collagen group of diseases and that observed in the heart and internal organs of human subjects dying with sulphonamide sensitivity, and with basically similar connective tissue cellular infiltrates produced in rabbits rendered hypersensitive to foreign serum protein. He tentatively suggests that the similarity between the mononuclear reactions of the diseases of known hypersensitivity and those of the collagen diseases connotes a common pathogenesis of these two entities.

In the search for the presence of an antigen in rheumatic diseases to account for the hypothesis that they may be hypersensitivity phenomena, Wichelhausen and colleagues[429] investigated the significance of pleuropneumonia-like organisms. They believe that the unique properties of human L organisms would satisfy the criteria of a persistent living antigen, invisible in tissues or invaded cells and not directly demonstrable as aetiologic agents. Their studies have indicated that twenty-eight strains of human L organisms show marked differences in sensitivity to anti-

biotics, gold salts and nitrogen mustard. Antibiotics effective *in vitro* are also effective *in vivo*, and this is manifest by disappearance of demonstrable organisms during administration of the orally active antibiotics and by transient exacerbations of clinical symptoms of collagenous diseases. The severity of the reaction parallels the *in vitro* effectiveness of the antibiotics and is not due to drug sensitivity. These workers believe such a reaction may represent a tissue response to antigen release in a system in which antibodies are readily available, and which can be modified by the administration of agents which interfere with hypersensitivity reactions. This is an interesting hypothesis which is worthy of further investigation. It cannot as yet be supported by serologic tests for L organisms owing to the difficulty of preparing satisfactory L antigens.

Humphrey and Pagel[192] investigated the tissue response to heat-killed streptococci in the skin of normal subjects and subjects with various rheumatic diseases, and made the interesting observation that "hypersensitive" types of response were obtained with one or more strain of streptococcus in the majority of rheumatic fever cases, subacute bacterial endocarditis, erythema nodosum and three of five cases of rheumatoid arthritis but not in normal subjects. These "hypersensitive" types of response had the characteristics of an Arthus type of reaction, with focal oedema, conglutination of collagen fibres, fibrinoid change and formation of fibrocytic nodules. In spite of the fact that bacterial antigens were used the reaction was more like that of serum hypersensitivity. The small number of the observations made do not at present justify any conclusive inference regarding hypersensitivity to streptococcal antigens in rheumatoid arthritis.

Cavelti[59,60] upholds the view that autoantibody formation may be an important factor in the causation of rheumatic diseases. He presents experimental data to show that autoantibodies to heart, connective tissue and skeletal muscle can be produced in rats and rabbits by immunizing them with emulsions of the homologous tissues in conjunction with killed streptococci. The streptococci render the autogenous tissues antigenic, with the formation of specifically active autoantibodies demonstrable *in vitro*. Rats immunised in this way develop changes in the valves and connective tissues of the heart which broadly resemble those of rheumatic carditis. Coburn[75] claims to have demonstrated antibodies to human tissues in rheumatic fever sera.

Unfortunately, hypotheses concerning autoantibody formation in the anaphylactic state are hard to substantiate owing to difficulties in their experimental production and demonstration. There is no human disease in which such a mechanism has been proved, although there is good evidence that this is the basis of many cases of acquired haemolytic anemia. Wallis[423] believes that his findings of greatly increased gamma globulins and the presence of abnormal T components in rheumatoid sera, estimated by electrophoretic and immunologic means, is evidence of a hyperimmune response, possibly to an autogenous tissue antigen. The ability of known connective tissue components to act as antigens would appear to indicate that they have no ability by themselves to provoke antibody formation. Hyaluronate from the ground substance of connective tissue is non-antigenic even after combination with horse serum albumin or when present as a protein hapten in the capsule of virulent streptococci.[191,262] Gelatin is known to be non-antigenic.[388] Hopps[187] could not demonstrate antibodies to purified collagen in the sera of rabbits immunised with catgut. Waksman and Mason[417] found that rabbit collagen and gelatin coupled with diazotized sulphanilic acid, and normal human collagen alone or coupled with human serum globulin was non-antigenic in rabbits, and they could not elicit an anaphylactic response to human collagen coupled with human serum globulin in guinea pigs. These authors also failed to demonstrate antibodies to human collagen by complement fixation and precipitin tests in the sera of nineteen patients with rheumatoid arthritis and other collagen-vascular diseases. Glynn and Holborow[141] have recently supplied important evidence that in the experimental animal autoantibody formation to a tissue polysaccharide can be elicited by its combination with a bacterial protein. In their experiments a vaccine prepared from group A haemolytic streptococci in the presence of chondroitin sulphate gave rise to rabbit antisera precipitating with this polysaccharide. Of six rabbits immunised with the vaccine five developed sterile arthritis with varying degrees of synovitis and perivascular cellular infiltrations, while in control animals receiving streptococci or chondroitin sulphate alone no such lesions developed. The authors refrain from drawing any definitive conclusions from

their experiments but the demonstration that streptococci can react with a connective tissue polysaccharide to produce antibodies enhances the possibility that autoantibodies to connective tissue components might be formed in disease states. Alternatively, this combination might be reversed; instead of the streptococcus providing the protein and the patient's tissues the hapten, the streptococcus may provide the hapten which renders tissue proteins antigenic. There is experimental evidence that pneumococcal polysaccharides can behave in this way.[16,17,144]

Green[150] supports the theory of the allergic basis of rheumatoid arthritis on different grounds. He has observed that corticotrophin and cortisone are powerful depressants of mitosis in mouse skin, and also reduce homologous and heterologous immunity to tumour growth.[151,152] These latter effects he believes are due to suppression of mitosis in precursors of the antibody-forming reticulo-endothelial cells. Such cellular inhibition could depress or abolish the tissue antigen-antibody reaction and the resultant allergic inflammatory response. This theory would account also for the suppression of the general effects of an allergic tissue reaction because of the failure of histamine and histamine-like metabolites to appear. It would also account for the non-specific nature of the ACTH-adrenal mechanism, and possibly also for the increased urate excretion and negative nitrogen balance induced by corticotrophin, because of the temporary cessation in nucleoprotein synthesis.

This suggested mode of action of corticotrophin in rheumatoid arthritis is not borne out by other studies attempting to relate its action in rheumatoid arthritis to tissue hypersensitivity of allergic type. The tissue response in known bacterial allergies, such as tuberculin hypersensitivity in guinea pigs, is strongly inhibited by cortisone and ACTH.[242] Postulating a possible analogy between this form of allergy and the tissue reaction in rheumatoid arthritis, Long et al.[244] suggested that other factors affecting experimental tuberculin hypersensitivity might also influence rheumatoid arthritis. However, Lovell, Osborne et al.[247] studied the effects of glucose-1-phosphate, lysergic acid diethylamide and ascorbic acid saturation,[243] all of which diminish or suppress experimental tuberculin hypersensitivity, in patients with rheumatoid arthritis, but found that both the arthritis and the subjects' reactivity to purified protein derivative of tuberculin were uninfluenced by these agents. These studies therefore failed to support the analogy between experimental tuberculin hypersensitivity and the tissue reaction in rheumatoid arthritis, though not refuting it.

RHEUMATOID ARTHRITIS AS A DISORDER OF ADAPTATION

From the work of Selye has arisen an entirely new conception of the pathogenesis of a number of diseases of unknown aetiology. This general concept Selye has called the "general adaptation syndrome" and the diseases concerned "diseases of adaptation."[361,363] Included among the disorders of adaptation are rheumatic fever, rheumatoid arthritis and other diseases involving primarily connective tissues. An extensive literature has grown up around the subject of the general adaptation syndrome, with much experimental evidence for and against it, but our chief concern is to examine whether rheumatoid arthritis can reasonably fit into this concept as Selye claims.

Briefly, Selye postulates that a wide variety of stresses or damaging stimuli, mediated through the pituitary, cause the production of adrenal steroid hormones whose function is the regulation of homeostasis. Normally the output of adrenocortical hormones regulating electrolyte and water metabolism (mineralocorticoids) is in some sort of equilibrium with those concerned in the regulation of carbohydrate metabolism (glucocorticoids). Selye believes that in disorders of adaptation the balance between the production of these two types of hormone is upset, and that the rheumatic diseases result from an excessive output of the electrolyte-regulating hormones relative to those concerned with carbohydrate metabolism.[361] Some evidence for this theory is provided by the observation of Selye and Pentz[364] that massive doses of 11-desoxycorticosterone (DCA) can cause in unilaterally nephrectomised rats on a high sodium chloride intake vascular and cardiac lesions similar to those occurring in periarteritis nodosa, hypertension and rheumatic fever, and it was suggested that abnormal, probably excessive, production of this type of hormone by the adrenal cortex was concerned in the causation of these diseases in man. Later[365] it was reported that exposure to DCA could produce an arthritis in similarly prepared rats if also adrenalectomised, thyroidectomised or exposed to cold. The

effect of the cold, thyroid and adrenal deficiency in these experiments was interpreted by the authors as to favour localisation of the action of the DCA to the joints. The resemblance of the arthritis in these rats to human acute rheumatism led to the tentative conclusion that the human disease might be a clinical manifestation of adrenocortical hypertrophy. By 1946 the theory that the rheumatic diseases, including rheumatoid arthritis, are disorders of adaptation was elaborated, and it was considered that they were due to adrenal cortex hypertrophy with an excess secretion of damaging mineralocorticoids with a DCA-like action. These changes were thought to be mediated through the hypophysis by its adrenocorticotrophic hormone, but the demonstration by Hench and the Mayo Clinic workers in 1949 of the beneficial effects of ACTH in rheumatoid arthritis and rheumatic fever necessitated a modification of the theory.[361] It was then suggested that mineralocorticoids are produced by the stressed adrenal under the influence of some other pituitary hormone, ACTH itself stimulating the production of the antirheumatic glucocorticoids, including cortisone and hydrocortisone (compound F). Selye reinterpreted his earlier findings concerning the effect of adrenalectomy on DCA-induced arthritis, suggesting that adrenalectomy sensitises to the toxic effects of DCA by removing the source of endogenous glucocorticoids, thereby predisposing to the development of an unfavourable glucocorticoid-mineralocorticoid ratio. He has also suggested that mineralocorticoids may be additionally deleterious by antagonising the action of glucocorticoids peripherally. In support of this revised theory he has cited his observations that an experimental "arthritis" can be produced in rats by injections of formalin around the joints, which is aggravated by pretreatment of the animals with DCA or crude anterior pituitary extracts, and suppressed by cortisone and corticotrophin.[362] That an anterior pituitary hormone may, in the absence of the adrenals, cause the production of an arthritis in the experimental animal is suggested from the work of Reinhardt and Li[319] who have recently succeeded in producing a chronic destructive polyarthritis in rats by repeated injections of a pituitary growth hormone intraperitoneally over long periods, the animals being prepared by preliminary adrenalectomy and oophorectomy, and maintained on 1 per cent saline solution. This arthritis was suppressed by cortisone. Non-specific sensitisation to the growth hormone cannot be excluded as the cause of the arthritis in these experiments and so no definitive conclusions are justifiable at the present time.

As regards rheumatoid arthritis, Bauer, Clark and Dienes[26] object to the Selye concept on the grounds that it is based on experimental arthritides in no way comparable to rheumatoid arthritis, and not always reproducible by other workers.[47,227,294] DCA in large doses does not aggravate rheumatoid arthritis in humans, even when considerable salt retention occurs, and the beneficial effect of cortisone is uninfluenced by the simultaneous administration of DCA. Also salt retention does not alter the effectiveness of ACTH. These observations are not in accord with Selye's theory. Marrian[253] takes exception to Selye's division of adrenal hormones into mineralocorticoids and glucocorticoids on the grounds that the pharmacologic evidence that the known active adrenal hormones can thus be classified is an unwarranted oversimplification of the known facts. He quotes work to demonstrate that such specificity of action of these steroids does not exist. Further he believes that evidence is lacking that such pharmacologic differences as have been observed between the active adrenal compounds have any biologic or physiologic significance. There may be no clear-cut distinction between the intrinsic biochemical activities of the 11-desoxy compounds on the one hand, and the 11-hydroxy and 11-keto compounds on the other, the observed differences in their effects being accounted for by differing rates of absorption, excretion and metabolism in the tissues. The work of Hechter et al.[172,173] indicates the possibility that 11-desoxycorticosterone may actually be converted into corticosterone *in vivo* in a manner similar to that demonstrated in adrenal perfusion experiments. Again, Selye regards compound S as a mineralocorticoid but Marrian points out that this steroid has actually less sodium- and chloride-retaining potency in dogs than has corticosterone, a glucocorticoid.[72]

Perhaps the strongest argument against Selye's theory is that rheumatic diseases in man are not usually accompanied by any significant disturbance of electrolyte metabolism as one would expect if excess production of DCA-like hormones were the prime cause. Few authenticated cases of rheumatoid arthritis have been reported in subjects with Addison's disease.[54,58,111,298,341]

There is also no increased prevalence of rheumatoid arthritis in cases of Simmond's disease (panhypopituitarism).[302]

Harrison[168] believes that the experimental arthritis produced by Selye et al.[365] in rats subject to left nephrectomy, increased sodium chloride intake and DCA injections, is explicable by localised necrosis of the adrenal cortex caused by interruption of the left adrenal artery during nephrectomy. In the rat adrenal histologic appearances can be correlated with adrenocortical function,[53,169] and interruption of an adrenal artery causes necrosis of part of the zona fasciculata.[167] Such a lesion would be expected to cause a decrease in "glucocorticoid" production, using the term in its physiologic sense, as this zone is responsible for the production of cortisone and other 11-keto corticosterones. Harrison describes experiments suggesting that, under the conditions described by Selye, arthritis during DCA injections develops only in rats possessing an area of focal necrosis restricted to the zona fasciculata of the adrenal cortex. His suggestion that DCA arthritis is partly dependent on the morphologic and functional state of the adrenal prior to and during the injections may be true, and if so vitiates any theory that such a mechanism is responsible for human rheumatoid arthritis, in which the adrenals show no structural abnormality.[382]

With regard to Selye's claim that ACTH and cortisone prevent the acute and chronic stages of experimental formalin "arthritis" in the rat, Parkes and Wrigley[290] found that, in their hands, formaldehyde failed to produce a chronic arthritis having the characteristics of human rheumatoid arthritis. The lesion produced by this agent was found by these workers to be exacerbated by DCA but not prevented by prior treatment with ACTH or cortisone. Bacchus,[18] however, found that ascorbic acid and cortisone both diminished the inflammatory response in formaldehyde-irritation "arthritis," and Dugal[103] found the lesion to be aggravated by cold and diminished by ascorbic acid in adult but not in young rats. The lesion produced in rats by para-articular formaldehyde injections is in the nature of a cellulitis, and may be accompanied by oedema elsewhere.[103] Bourne,[41] from a histologic study of the lesion produced in the manner of Selye, found it to be a severe periarthritis, without extension of the inflammation into the joint itself, which healed spontaneously in a month. The lesion was in no way comparable to rheumatoid arthritis.

True chemical arthritis is histologically nonspecific, and may be produced by a number of unrelated compounds. Jordan[198] produced a sterile monoarticular synovitis in rabbits by the intra-articular injection of xylene and turpentine, and noted the close similarity of the lesion to that of naturally occurring rheumatoid arthritis. Hyaluronidase and mustard powder have also been used to produce a similar lesion. In Canada investigators working with aqueous suspensions of mustard have produced granulomas and pannus formation in animal joints, cartilaginous erosion and ankylosis ensuing in about half the cases. It is of interest that experimentally induced chronic arthritis can be inhibited by hormone therapy but this effect is certainly non-specific, being related to the general anti-inflammatory action of cortisone.

It cannot be said thus far that the experimental production of arthritis in animals by bacterial, chemical or hormonal agents has thrown any light on the mechanism of rheumatoid arthritis in man, except to indicate that the capacity of synovial tissues to react to a wide variety of injurious stimuli is sharply limited, with a narrow range of specificity.

The cortisone-like action of large amounts of ascorbic acid in these experimental lesions[18,45,103] is of interest as cortisone has been found to be antiscorbutic in guinea pigs, while DCA aggravates the lesions of experimental scurvy.[347] The essential role of ascorbic acid in connective tissue formation is discussed elsewhere but it should be noted that the antirheumatic (or, more strictly, anti-inflammatory) effects of ascorbic acid has been described only in intact, and not in adrenalectomised, animals. This suggests the possibility that the action of ascorbic acid in these experiments may be related in some way to the production of endogenous cortisone, as there is a clear relation between ascorbic acid and adrenocortical activity.[346] Ascorbic acid in massive dosage has been claimed to have "antirheumatic activity"[255] but opinions are conflicting. No primary deficiency of ascorbic acid has been found in subjects with rheumatoid arthritis.

Thus it may be said that, while Selye's theory of rheumatoid arthritis as a disorder of adaptation is both original and provoking, the evidence for it is at present based solely on somewhat controversial animal experiments, and there is as yet no good evidence that such a sequence of

metabolic disorders as Selye postulates does occur in the human subject with rheumatoid arthritis.

STEROID HORMONES AND THEIR RELATIONSHIP TO RHEUMATOID ARTHRITIS

Investigation into the pathogenesis of the rheumatic diseases was greatly stimulated by the discovery of the anti-rheumatic effects of pituitary adrenocorticotrophic hormone (ACTH) and 17-hydroxy-11-dehydrocorticosterone (cortisone).[179] The reasoning which eventually led to the use of cortisone and ACTH in rheumatic diseases is outlined by Hench in his Nobel lecture.[178] The unpredecented opportunities for research which the use of these hormones offered were early recognized,[387] and largely as a result of their use the old descriptive and empiric approach to the rheumatic diseases has been replaced by more physiologic thinking and by modern biochemical and biophysical methods of investigation.

Conditions other than rheumatoid arthritis and rheumatic fever in which the hormones are capable of inducing remission, or the manifestations of which may be suppressed by their use, include the connective tissue diseases, especially disseminated lupus erythematosus and some cases of periarteritis nodosa, several types of allergic and hyperergic reactions, acute gout, acute and subacute inflammatory diseases of the eye, and a number of diseases of unknown aetiology.[178]

Much detailed observations has accompanied the clinical application of the hormones in diseased states and considerable data have accrued concerning their general metabolic and local tissue effects in subjects with rheumatic and hypersensitivity states and other inflammatory conditions. As a result the mode and site of action of the hormones is becoming more clearly defined, and it is becoming increasingly evident that their action is in no way specific. Although capable of exerting a profound depressant action on connective tissue reactivity, neither hormone can permanently eradicate the basic inflammatory state of the mesenchymal tissues in rheumatic states.

Metabolic Changes. Both ACTH and cortisone in large doses exert a profound influence on electrolyte metabolism in healthy subjects and patients with rheumatic diseases.[125,254,312] ACTH causes a negative balance for nitrogen and potassium, with simultaneous retention of sodium and chloride, superseded by an increased excretion of those ions with the development of a hypochloraemic, hypokalaemic alkalosis. Cortisone in antirheumatic doses over several weeks can cause a significant alteration in the plasma electrolyte concentration and nitrogen balance. Occasionally the plasma potassium may fall below 3 mEq./L. Retention of sodium is accompanied by a gain in weight. The electrolyte shift returns to normal when the hormones are discontinued, and may be minimized or abolished by a low dietary intake of sodium, added dietary potassium salts and the administration of testosterone propionate as an anticatabolic agent. The hormones also increase urate excretion and rather irregularly cause creatinuria and lower the serum level of inorganic phosphate. These changes are also reversed when the hormones are withdrawn. The antirheumatic effects of the hormones are clearly not related to these electrolyte changes, as they cannot be reproduced by the 11-desoxysteroids, which produce the same pattern of electrolyte changes,[70] and most cases of rheumatoid arthritis can be maintained in remission for long periods by amounts of cortisone insufficient to cause detectable electrolyte or nitrogen imbalance.

Similarly the haematologic effects of the hormones (leukocytosis, eosinopenia, reticulocytosis, an increase in circulating haemoglobin and correction of anaemia[117]) and their occasional effects on carbohydrate metabolism—transient renal glycosuria and transient reduction of carbohydrate tolerance—[81] cannot be held to account for their antirheumatic activity.

Laboratory manifestations of rheumatoid arthritis which are corrected temporarily by hormone therapy are the elevated erythrocyte sedimentation rate, elevated serum globulin and plasma fibrinogen,[411] lowered urinary amino acids,[43] elevated serum non-specific hyaluronidase inhibitor and serum mucoproteins of Winzler.[1] None of these abnormal laboratory findings are pathognomonic of rheumatoid arthritis and appear to be related to the activity of the disease process, returning toward normal in any remission, whether spontaneous or induced. Depression of the erythrocyte sedimentation rate by ACTH occurs even in normal subjects, due to a lowering of the plasma fibrinogen.[115]

Immunologic Effects. The hormones do not significantly or constantly alter the titre of agglutinins to group A haemolytic streptococci

in the sera of patients with rheumatoid arthritis, nor the differential titre of agglutinins against sensitised sheep erythrocytes.[208,312,400] These agglutination phenomena are most likely an integral manifestation of the disease rather than a host response which can be non-specifically modified by the hormones.

Histologic Effects of Steroids in Rheumatoid Arthritis. Articular biopsies of synovia carried out before and at varying times during hormone therapy of rheumatoid arthritis reveal varying degrees of improvement, in some instances very striking, consisting of a reduction in oedema, vascularity and mononuclear cellular infiltrations, but without restitution of the membrane to complete normality.[28,180,281] Clark, Ropes and Bauer[70] found no histologic changes in rheumatoid nodules during and after ACTH treatment but Ragan, Grokoest and Boots[312] found them to become smaller with treatment; and although there is a general reduction in the number of lymphocytes and plasma cells present, the fibrinoid remains unchanged. These findings have been confirmed by other workers[180,208,281] but Hunt and Blanchard,[193] and Fienberg and Colpoys[116] both claim a reduction in fibrinoid as well as involution of the cellular content of rheumatoid subcutaneous and scleral nodules following treatment, with further development afterward. The cellular and degenerative muscular lesions have been observed to be diminished or disappear in treated cases.[281]

The evidence to date concerning the effects of hormones on the histopathologic lesions suggests that they have little or no effect on fibrinoid as such, the principal effects being an inhibition of new collagen formation and suppression of the vascular and cellular components of rheumatoid inflammation.

Observations on the effect of hormone treatment on the synovial fluid in rheumatoid arthritis indicate a suppression of the inflammatory process which is most rapid and striking when hydrocortisone is injected directly into the joint.[186,441] The volume of fluid diminishes, the leukocyte count falls, glucose levels when low rise; and there is a tendency for the total protein content to fall and the proportion of albumin to rise.[70,80,139] Ziff and others[441] point out that measurement of the proteolytic enzyme aminotripeptidase, which is especially high in rheumatoid fluids and is associated with a high leukocyte count, is a good index of the inflammatory state of the joint tissues. The concentration of this enzyme is lowered by hormone treatment concurrently with the reduction of other indices of inflammation.

Perhaps the most striking change in the synovial fluid is the increase in viscosity and the return of a normal mucin clotting effect after acidification. This might suggest a reversion of the synovial hyaluronate to a more highly polymerised state, in accordance with the theory of Ragan and Meyer[314] that the hyaluronate of rheumatoid fluid is relatively incompletely polymerised. It cannot be accounted for by an increase in glucosamine concentration.[441] But whether the rise in viscosity can be interpreted as a specific effect of cortisone or hydrocortisone is doubtful, as reduction of inflammation alone may cause a similar effect. Together, reduction of inflammation and of capillary permeability[335] by cortisone could account for all the changes observed in the treated rheumatoid synovial fluid.

Effects of Steroids on Connective Tissues. Ragan and others drew attention to the fact that wounds heal poorly in hyperadrenal patients, and that open wounds and abscesses do not granulate normally and heal slowly in patients receiving ACTH.[312] In rabbits,[23,313] mice,[385] rats[23] and in man[84] ACTH depresses the formation of granulation tissue in experimental wounds. Plotz and his colleagues, and Ragan have shown that experimental incised wounds in rabbits show delayed healing under the influence of cortisone, apparently due to an absence of fibroblasts and capillary proliferation. Epithelial regeneration occurs, apparently normally. These effects are partly dependent in degree on the amounts of cortisone given. Experimental fractures in cortisone-treated rabbits show delayed absorption of the traumatic haematomata and delayed callus formation. Observations on human subjects with surgical wounds while under hormone treatment have not been unanimous in regard to healing and repair, at any rate with therapeutic dosages. The means whereby cortisone inhibits connective tissue formation is not known. Ragan[311] believes that cortisone affects the fibroblast precursors, and Shapiro et al.[368] believe, from their observation that locally applied cortisone inhibits granulation tissue formation, that the action is directly on the growing fibroblasts or on the matrix in which they develop. Selective injury to fibroblasts is reported by Schneebeli.[350] Layton[229,230] postulates that cortisone inhibits synthesis of chondroitin sulphate. Deposition of mucopolysaccharides

in the tissues is an essential precursor of collagen formation, and cortisone has been shown to suppress the formation of metachromatic material in healing wounds,[313,386] and the fibrous reaction to insoluble foreign particles.[86,249] The steroids also reduce the hyaluronic acid in skin connective tissue and reduce the number of mast cells which probably form it.[14]

Roberts et al.[328] found that cortisone injected into embryonated hens' eggs caused an increased concentration of free hydroxyproline in the tissues of the embryo, and interpreted this as being due to inhibited synthesis of collagen in the tissues. Tissue culture experiments by Gerarde and Jones[135] have also shown that cultures prepared from cortisone-treated embryos show prolonged inhibition of collagen production in media containing cortisone. Bangham,[23] as a result of studying the effects of cortisone on wheal formation in the skin of rabbits after injecting solutions of histamine and leukotactic peptides, tentatively relates the inhibitory action of cortisone on granulation tissue formation to its apparent ability to protect small blood vessels from substances increasing their permeability.

A vital study of the microscopic effects of cortisone on connective tissue reactivity in rabbits with non-specific inflammation, bacterial allergy (tuberculous infection in the tuberculin-sensitised animal), and anaphylactic hypersensitivity (serum sickness) by Ebert and Barclay,[108] using the ear-chamber technique, shows that in all these inflammatory reactions, specific and non-specific, the effect of cortisone is the same. In treated animals it maintains vascular tone, reduces damage to arteriolar and venular epithelium and, as a result of the increased integrity of the vascular endothelium, decreases cellular and humoral exudation regardless of the type of inflammatory stimulus. The normal inflammatory response returns when cortisone is withdrawn. A similar suppression of all components of the earliest phases of the inflammatory reaction, with reduction of vascular margination of leukocytes, diapedesis, and oedema and fibrin formation, was observed by Michael and Whorton[266] using croton oil and scarification as the inflammatory stimulus in the skin of rabbits. Menkin[261] shows that, in the experimental animal, intravenous cortisone can enter a focus of acute inflammation and exert a suppressive action due, he believes, to its inhibition of the action of leukotaxine in increasing capillary permeability and inducing leukocytic migration. This local accumulation of cortisone would, he thinks, explain its action in rheumatoid arthritis. ACTH has a pronounced effect in reducing capillary permeability in man.[335] The hormones have also been shown to reduce the local and systemic inflammatory reactions to bacterial and viral infections,[202,203] to depress or abolish the Shwartzman phenomenon,[379] to depress experimental hyperergy and the Arthus phenomenon[136] and to inhibit the response to tuberculin[242,395] and atropine[246] in sensitised subjects. Quantitative immunochemical studies by Fischel and his colleagues have demonstrated a diminution of circulating antibodies after administration of cortisone and ACTH to rabbits, probably due to an inhibitory effect of the hormones on antibody synthesis.[35, 119,120] Cortisone also markedly inhibits the rapid production of antibody associated with the specific anamnestic or secondary response.[121]

It appears certain from these observations that the antirheumatic activity of cortisone and ACTH is a local, non-specific depression of connective tissue reactivity to noxious stimuli. This action appears, at least in part, to be on the connective tissue constituents directly. There is convincing evidence that the vascular apparatus is profoundly influenced from the beginning of the inflammatory response but the effect on connective tissue cells and interfibrillar ground substance is less clear. The observation that under the influence of ACTH or cortisone hyaluronate of synovial mucin regains its viscosity has no significant implications in this respect. The anti-inflammatory and antirheumatic effects of cortisone cannot be accounted for by an antihistaminic action, as local histamine responses are unaltered by cortisone or ACTH.[232,245,246] Evidence for depression of serologic antibody formation by cortisone is as yet incomplete and cannot be appraised in its significance to rheumatic disease. The exact significance of the anti-hyaluronidase effects of steroids on connective tissues[287,288,352,358,431] in rheumatic states is obscure.

Knowledge concerning the influence of ACTH and cortisone on various enzyme systems throughout the body is still too fragmentary to throw any light on their mode of action in rheumatism, but it would seem that the rate of most enzyme reactions studied in animals given cortisone is increased. It is of importance that Umbreit[408] has clearly demonstrated that in rat

tissues the oxidation of proline and hydroxyproline, both major constituents of collagen, is in some sites under the action of cortisone.

Thus one may conclude that although the adrenal steroids profoundly modify the reaction of mesenchymal tissues, these effects are not confined to rheumatic states but occur in any condition in which the response of the tissues to injury is altered. Detailed study of the action of these compounds has not revealed the nature of the basic inflammatory stimulus in rheumatoid arthritis.

CONCLUSIONS

It will be evident from this survey that although factual data have accrued concerning the pathogenetic mechanisms of rheumatoid arthritis, the factors predisposing to, precipitating and maintaining the inflammatory state in this disease are still unknown. However, recent work has suggested several promising leads worthy of exploration.

Pathologic studies in rheumatoid arthritis have clearly indicated that the disorder is much more than merely a polyarthritis; it is a generalized affection of connective tissue structures of a more widespread nature than is evident from clinical findings alone. In spite of intensive and critical study by all practicable techniques, the nature of the characteristic pathologic change—fibrinoid—remains undefined. The newer concept of rheumatoid arthritis as being one of a group of diseases—the connective tissue diseases, or collagenoses—linked by the site and nature of their primary lesion, and by some common clinical manifestations, is undoubtedly a step forward in our understanding of the nature of the disease but does not necessarily imply the concept of a unified aetiology for the whole group. Some indication has been given of the present state of knowledge of the physiology, structure, composition and reactivity of the fine connective tissues and their components but the application of these data in rheumatoid arthritis is sharply limited by its incompleteness in the normal state, and by present ignorance of the changes occurring in disease.

Theories of direct bacterial infection of the inflamed tissues in rheumatoid arthritis are now virtually untenable, and the evidence for a viral aetiology, although unlikely, cannot be excluded with absolute certainty. The discovery that the sera of many patients with rheumatoid arthritis have the ability to agglutinate heterologous erythrocytes sensitised with antibody is of prime importance for three reasons: first, because of the high degree of specificity of the test for rheumatoid arthritis; second, because this property of the serum appears to be an integral component of the morbid process which, when once present, is uninfluenced by changes in the general inflammatory state; and third, because it appears to be related to the presence of fibrinoid in the tissues. Further investigation of this phenomenon, and of the formation of fibrinoid, seems likely to be rewarding in elucidating the nature of the fundamental rheumatoid defect.

Theories of avitaminosis and of primary disorders of sulphur and carbohydrate metabolism and of hepatic dysfunction have little to commend them. Such metabolic defects of this nature as have been found are almost certainly *post hoc* and aetiologically insignificant. While there is clear evidence that an altered immunologic response to extrinsic allergenic factors is directly concerned in the pathogenesis of some of the closely related disorders in the group of connective tissue diseases, the evidence presented by the proponents of this theory is still circumstantial and inferential in the case of rheumatoid arthritis, and an offending antigen, whether extrinsic or intrinsic, has yet to be proven. Much the same might be said about the theory of rheumatoid arthritis as a disorder of adaptation, with the added argument that the experiments on which this concept is largely based are generally of such a nature as to be inapplicable to pathologic states in the human organism.

Of great interest and importance are the recent observations of structural changes in the adenohypophysis and of altered adrenocortical steroid metabolism in cases of rheumatoid arthritis but this work is in too early a stage, besides requiring further confirmation, to permit its application to aetiologic theories at this time. The ability of the steroid hormones to suppress the manifestations of rheumatoid arthritis has yielded no direct aetiologic information but the hormones remain an important instrument in the study of pathogenetic mechanisms.

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Seminars on the Hemolytic Anemias

The Metabolism of Hemoglobin and Bile Pigment in Hemolytic Disease*

LT. COL. WILLIAM H. CROSBY, M.C.
Washington, D. C.

"HEMOLYTIC jaundice" and "hemolytic anemia" were accepted as clinical equivalents for many years. In the nineteenth century it was known that bilirubin was the cause of jaundice, that hemoglobin was the source of bilirubin and that hemolytic jaundice was due to excessive destruction of red cells and their hemoglobin. Gray has written an accurate and concise history of the development of this interesting subject.[11] In recent years the use of chemical and isotopic methods has taught us much about pigment metabolism. Needless to say we have also learned that this is a field of endless complexity. Five years ago a review of the subject was published by Lemberg and Legge in a book of 1,400 pages.[15] The present summary of the information that bears upon the problem of hemolytic disease suffers necessarily from oversimplification. It is intended as an approach for the clinician who seeks to understand the mechanisms underlying "hemolytic jaundice."

Pigment metabolism is dynamic. Although the concentration in the blood of hemoglobin and bilirubin is constant, the constituent molecules of these pigments are always changing. The mean life span of the normal red cell is 120 days. In mature red cells no hemoglobin is formed or destroyed; therefore the life span of hemoglobin molecules is the same as that of the red cells in which they ride. On the other hand, the life span of bilirubin molecules in the plasma is only ninety minutes. The unchanging level of pigment in these dynamic systems clearly indicates that a precise balance exists between gain and loss. Production and destruction are in equilibrium.

In hemolytic disease,† although the average life span of the red cells is reduced, the same sort of balance exists. In an effort to prevent anemia the bone marrow increases the production of red cells and hemoglobin. Thus more hemoglobin is destroyed, more is produced, the turnover is rapid and, excepting times of crises, the concentration of hemoglobin in the blood remains constant.

A simple formula can be applied to this sort of situation:

$$M = PL$$

M is the total quantity of the substance in the circulating blood. If the concentration of the substance is the same in all parts of the circulation this figure can be derived by multiplying concentration by total blood volume. P is production or the amount of the substance that enters the circulation per unit of time. L is the average life span of particles of the substance in the circulation expressed in units of time.

To demonstrate the turnover of hemoglobin in a normal man who weighs 70 kg. we substitute the following values in the formula.

† Throughout this discussion three terms are used: hemolytic disease, hemolytic anemia and hemolytic jaundice. They are not equivalent. Hemolytic disease occurs when, in the absence of hemorrhage, the average life span of the circulating red cells is less than normal. Hemolytic anemia occurs when the bone marrow, by increased production of red cells, is unable to compensate completely for the shortened life span. Hemolytic jaundice occurs when such quantities of bilirubin are presented to the plasma that the normal excretory capacity of the liver is unable to maintain a normal concentration of bilirubin in the plasma. Hemolytic disease may exist with no anemia or jaundice.

* From the Department of Hematology, Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D. C.

M = 750 gm. of hemoglobin in his circulating blood.
P = 6.25 gm. of hemoglobin produced each day (90 mg. per kg.).
L = 120 days, which is the average life span of the red cells and hemoglobin.

In a man of the same size who has hereditary spherocytosis typical values will be these:
M = 500 gm. of hemoglobin, indicating a moderate anemia.
P = 41.66 gm. of hemoglobin produced each day (600 mg. per kg.).
L = 12 days. The average life span of the red cells is about $\frac{1}{10}$ of the normal.

It can be seen that the production of hemoglobin in hereditary spherocytosis is more than six times the normal, which is an index to the capacity of the bone marrow to respond to the stimulus of hemolytic disease. It can also be seen that the patient producing this amount of hemoglobin would not have been anemic were the average life span of his red cells eighteen days instead of twelve. Here is an important concept in the pathogenesis of hemolytic anemia. The bone marrow is often able to compensate completely, and there is no anemia, when the average life span of the red cells is more than twenty days. When it is less than that, anemia is usually present and the severity of the anemia is proportional to the life span of the red cells. The bone marrow reaches the limit of its ability to compensate when it produces six to eight times the normal amount of hemoglobin. When the demand exceeds this we find hemolytic anemia.[2]

In some forms of hemolytic disease the bone marrow is unable to achieve this degree of response. This is true of Cooley's anemia, pernicious anemia, nocturnal hemoglobinuria and diseases in which the marrow is partially replaced by fibrous tissue or neoplasm. In these diseases the output of hemoglobin may be greater than normal by three or four times but anemia is present even though the average life span of the red cells is more than twenty days.[4]

Changes in the concentration of hemoglobin occur in hemolytic disease during periods of crises.[2] The crises are of two sorts: In *aregenerative crisis* the bone marrow may abruptly cease the production of red cells while destruction continues at the usual abnormally rapid rate. In *hemolytic crisis* the life span of the red cells is reduced to an even greater extent. In both crises the effect on the circulating hemoglobin is the same and the patient becomes more anemic. In both crises the destruction of red cells *temporarily* exceeds production. It is important to understand that this is a temporary imbalance, for if it continued the patient would soon have no red cells at all. During recovery from such crises the opposite is true. Production temporarily exceeds destruction until equilibrium is achieved. When the size of the mass of circulating red cells remains constant, production and destruction must be in equilibrium.

Increased Production of Hemoglobin. There are two mechanisms whereby the marrow might increase its output of red cells and hemoglobin. The first is to increase the amount of erythropoietic tissue. This is accomplished by increasing the concentration of red cell precursors in the marrow and by expanding the volume of active marrow. In the normal "red marrow" about one of every six nucleated cells is erythroid. In hemolytic anemia the concentration is increased so that three of six nucleated cells may be erythroid.[6] Areas of "yellow marrow" that are ordinarily fatty and inactive are invaded by hematopoietic cells, thus doubling the volume of functioning marrow. Taken together these two enlargements of the erythropoietic organ serve to increase sixfold the number of erythroid cells in the marrow.

The second possible mechanism for increasing red cell production is to hasten the process. It is difficult to imagine how this would be effected, for it implies that the synthesis of protein would be accelerated. There is no evidence that it does occur. In severe hemolytic disease the marrow may release large numbers of immature red cells but this does not increase the speed of maturation and it does not increase the output of the marrow any more than marketing green apples increases the yield of an orchard.

The maturation of red cells in the bone marrow is essentially a process of hemoglobin synthesis.[24] In the early phases of erythropoiesis there is much evidence of metabolic activity in the young erythroblast. The nucleus is large, occupying almost the entire cell. Mitoses are frequent. In the cytoplasm are mitochondria whose presence indicates intense metabolic activity. The presence of the basophilic ribonucleic acid is evidence of active protein synthesis, and globin is the protein being produced. When the actual synthesis of hemoglobin gets under way, the cytoplasm becomes more and more acidophilic. The cell meanwhile becomes smaller, the nucleus

and its chromatin are more compact and mitoses are less frequent. The mitochondria seem to agglutinate and then disappear. With protein production nearing completion, the basophilic ribonucleic acid fades from the cytoplasm. The cell continues to shrink, to become more compounded of iron, protoporphyrin and protein. The iron-protoporphyrin complex, called *heme*, occurs not only in hemoglobin but also in myoglobin and in other intracellular respiratory pigments such as cytochrome and peroxidase. The family of porphyrins is a large one but all

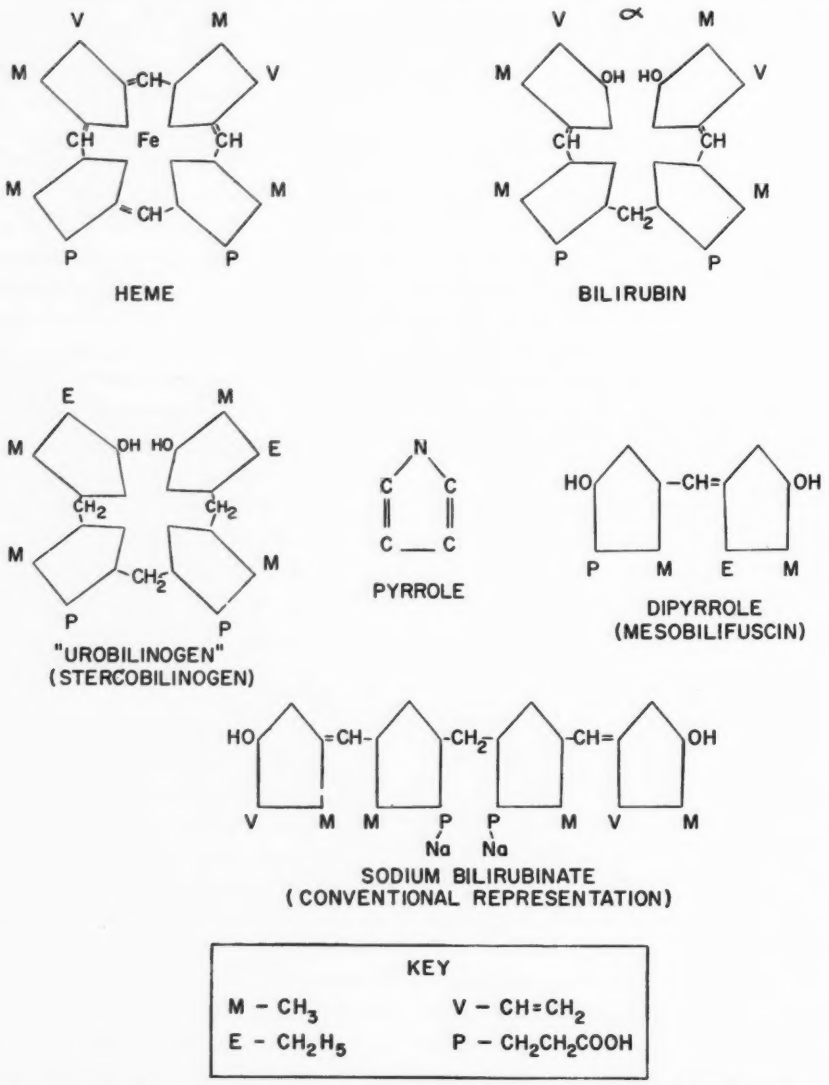

FIG. 1. The chemical structure of heme and representative bile pigments.[15] Note that bilirubin differs from heme in that iron is gone and the alpha methene bond is broken. Bilirubin is usually represented as a straight chain compound but it is probable that the chain has a circular configuration.

pact; its margins are more definite and, except for its pyknotic nucleus, it takes on the appearance of a mature red cell. With the nucleus finally extruded the cell is ready for delivery to the circulating blood. With proper staining a small amount of ribonucleic acid appears as the "reticulum substance" of the reticulocytes.

Construction of Hemoglobin.[7] Hemoglobin is one of the family of respiratory pigments com-

are similar in structure. They are composed of four pyrrole nuclei bound together by methene bonds. (Fig. 1.) At the periphery of this molecule are eight substitution points. The different porphyrins are formed by isomeric changes in the kind and combination of substituents inserted at these points. The combinations are of four basic types. When four methyl and four ethyl groups are placed appropriately at the eight

substitution points, four isomeric compounds are possible. These isomers are called *etioporphyrins* I, II, III and IV. All other porphyrins are classified according to these four patterns. Take for example one important member of the family, *protoporphyrin.* In this compound the pattern is that of etioporphyrin III. The methyl groups are the same but the ethyl groups are replaced, at the north of the molecule by vinyl groups, at the south by propionic acid. (Fig. 1.)

Protoporphyrin is the molecule that combines with iron to form heme:

Protoporphyrin + iron → heme
Heme + globin → hemoglobin

In all heme-combined respiratory pigments, such as myoglobin, cytochrome, hemoglobin, etc., the heme molecule is the same. It is the quality of the protein, globin, that distinguishes hemoglobin from the others. The globin molecule is probably cylindrical in shape, its diameter somewhat greater than its height.

Globin (molecular weight 68,000) makes up 96 per cent by weight of the hemoglobin molecule. To each molecule of protein are bound four molecules of heme (molecular weight 600+). The four hemes behave identically in all hemoglobin reactions, suggesting that they are arranged symmetrically on the globin molecule. They are probably attached at or near the surface as flat, plate-like structures. They are pigments and they impart to hemoglobin its characteristic red color.[10]

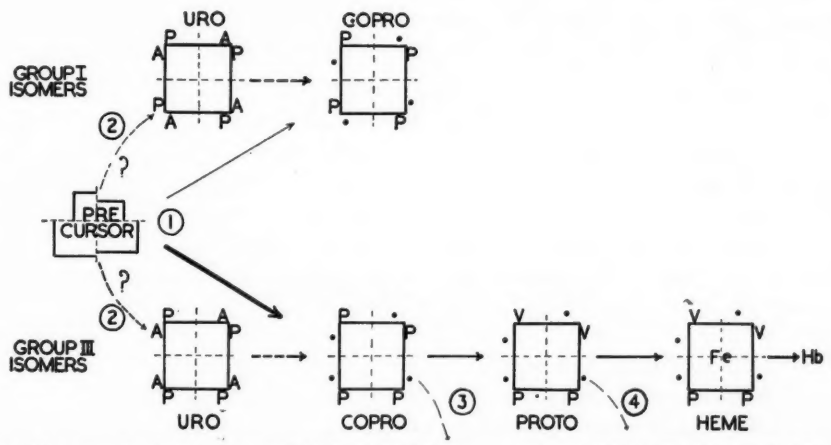

FIG. 2. Biosynthesis of the porphyrins. A = acetyl (CH_2COOH). P = propionyl (CH_2CH_2COOH). V = vinyl ($CH=CH_2$). Dot = methyl (CH_3). Each corner of a square represents the two substitution points of a pyrrole nucleus. (Fig. 1.) The reactions represent decarboxylation. The acetyl groups of uroporphyrin are decarboxylated to form coproporphyrin and the "northern" propionyl groups of coproporphyrin are decarboxylated to form protoporphyrin. The precursors are compounds of acetic acid and glycine, the raw materials from which all porphyrins derive. Uroporphyrin has only recently been isolated in the normal human body and its role has not yet been clarified. The step indicated by the broken arrow is therefore speculative. If it occurs, it is very rapid and the body is effectively protected against interruption of the reaction at this point. In porphyria the reaction jumps the track somewhere near point 2. Either porphyrin synthesis is abnormally channeled in that direction or, if it is indeed a normal channel, the reaction is interrupted here and uroporphyrin appears in large quantities. There is also excessive excretion of coproporphyrins I and III. The normal synthesis of porphyrin is heavily weighted in favor of groups III, as indicated by the heavy arrow at point 1. The formation of isomers, I and III, though different in amount is proportional. When hemoglobin synthesis is increased, as in hemolytic anemia, coproporphyrin I in the urine is also increased. Not all coproporphyrin III becomes protoporphyrin, and not all protoporphyrin becomes heme. Traces of both are to be found in young red cells (erythrocyte coproporphyrin and erythrocyte protoporphyrin). These frustrated porphyrin molecules are indicated by the dotted arrows at points 3 and 4. Lead poisoning results in increased excretion of coproporphyrin III. It is believed that lead may block the reactions at point 3 to inhibit formation of protoporphyrin and heme. In thalassemia there is also inhibition of hemoglobin synthesis, for in the hypochromic red cells one finds not only an excess of erythrocyte protoporphyrin but also granules of siderin indicating an excess of iron.

In the synthesis of heme, protoporphyrin is elaborated from glycine and acetic acid.[19,20] Iron is added to the protoporphyrin to form heme which then combines with the globin molecule. (Fig. 2.)

"Trace Porphyrins" in Hemolytic Disease.[28] In the process of hemoglobin synthesis porphyrins other than protoporphyrin appear. (Fig. 2.) Some of these, such as coproporphyrin III, appear to be precursors of protoporphyrin. Others, such as coproporphyrin I, are apparently by-

products of hemoglobin synthesis. Young red cells contain measurable amounts of coproporphyrin III so that in hemolytic disease, in which young cells abound, the amount of "erythrocyte coproporphyrin" is increased. Young cells also contain traces of protoporphyrin and in hemolytic disease the amount of erythrocyte protoporphyrin also is increased. As red cells mature they lose both of these porphyrins; the coproporphyrin is rapidly lost, the protoporphyrin slowly.[28] The amount of coproporphyrin I produced by the body is proportional to the production of hemoglobin. This pigment is apparently useless and is excreted in the urine, usually 100 to 300 gamma per day, but with the intense erythropoiesis of hemolytic disease the daily excretion of coproporphyrin is 200 to 400 gamma.[30]

Degradation of Hemoglobin. Bile Pigment Metabolism:[15] When red cells are destroyed in the normal fashion, the hemoglobin is totally degraded and its three constituent parts, protein, iron and porphyrin, go their several ways. None of the hemoglobin is reutilized as such. The protein is returned to the body's "protein pool" and its amino acids are used for construction of new proteins or for other metabolic requirements; some of it may even find its way into the globin of a new hemoglobin cycle. Similarly, the iron is returned to the "iron pool" but because this pool is small and most of the body's iron is needed for hemoglobin, the iron from old hemoglobin quickly finds its way into new red cells. The porphyrin fraction of the degraded hemoglobin is not reutilized at all. The preponderance of evidence indicates that the entire molecule is excreted as bile pigment of one sort or another. (Figs. 1 and 3.) The normal destruction of hemoglobin is believed to occur in the phagocytic cells of the body, the so-called reticuloendothelial system, and the bilirubin is formed in these phagocytes. From the phagocytes the pigment is carried in the plasma bound to albumin or alpha globulin.[12] In the liver the pigment molecules are stripped from the protein and excreted into the bowel as sodium bilirubinate.

Once in the bowel the bilirubin is further altered by the action of intestinal bacteria to form several degradation products (mesobilirubinogen, d-urobilin, d-urobilinogen, mesobilene-b, stercobilinogen, stercobilin and probably others). All are lumped together when we speak of "fecal urobilinogen." These pigments are measured by the red color that is produced with Ehrlich's aldehyde reagent after they have undergone reduction. During the journey along the colon about 50 per cent of the urobilinogen is resorbed, recirculated in the blood and reexcreted by the liver. (Fig. 3.) This is the source of urobilinogen in liver bile and the small amount lost through the kidney as "urinary urobilinogen."

It is probable that the degradation of bilirubin does not stop with "urobilinogen." Further destruction of these tetrapyrrolic compounds produces dipyrroles and even monopyrroles. (Fig. 1.) Some evidence indicates that at least four dipyrroles found in feces may be degradation products of bilirubin.[23] These dipyrroles do not give red color with Ehrlich's aldehyde reagent. The importance of this will be considered later.

The amount of bile pigment produced each day in the normal human body is closely related to the amount of hemoglobin that is created and destroyed.[4] The porphyrin moiety, exclusive of iron, makes up 3.5 per cent by weight of the hemoglobin molecule. Since protoprophyrin and bilirubin have practically the same molecular weight (Fig. 1), it is easy to see that destruction of 1 gm. of hemoglobin should make available 35 mg. of bilirubin. Experiments in animals with bile fistulas have shown that this amount of pigment can actually be recovered.[14] From this basis we can compute the amount of bile pigment that is formed each day from the normal destruction of worn-out red cells. A man of 70 kg. who each day produces and destroys 6.25 gm. of hemoglobin should therefore produce about 220 mg. of bilirubin. But worn-out cells are not the only source of bile pigment. When glycine tagged with isotopic nitrogen (N^{15}) is fed to normal men, some of the N^{15} is used to form the pyrrole rings of hemoglobin porphyrin. When this hemoglobin is destroyed at the end of the red cells' life span, the N^{15} is found in the fecal urobilinogen at that time.[21] This is as one might expect. However, during the time that these N^{15}-tagged red cells are being formed in the bone marrow there appears in the feces a surprisingly large amount of N^{15}-tagged urobilinogen: 10 to 20 per cent of the daily output.[13,16] The source of this pigment is not known. Some of it probably comes from non-viable red cells, cells that fail to meet rigid specifications for size and shape and are therefore rapidly destroyed. Other sources of "early appearing urobilinogen" have been proposed.[11,16] (1) It is possible that more

protoporphyrin is formed by the erythroblast than is needed for hemoglobin and the excess is degraded to bilirubin. Evidence for this is found in the traces of erythrocyte protoporphyrin present in immature red cells, as already mentioned. (2) During the period of rapid hemoglobin synthesis in the erythroblast some hemoglobin may be destroyed. This has been suggested because there is some evidence to indicate that the synthesis of other proteins is associated with a certain amount of protein destruction. (3) Bilirubin may be produced as such in the process of porphyrin synthesis. There is no evidence for this. (4) Other porphyrin pigments such as cytochrome may have a much more rapid cycle than hemoglobin. There is no evidence for this. Although the source of the early appearing urobilinogen is unknown, its existence indicates that the total bile pigment produced each day by a 70 kg. man exceeds by 10 or 20 per cent the 220 mg. derived from worn-out red cells. Thus the total daily bile pigment production in this man would be about 250 mg.

The amount of urobilinogen found in the feces does not equal the amount that would be there if all bilirubin were converted to urobilinogen and all of this were extracted and measured by Ehrlich's aldehyde reagent. The normal daily values for fecal urobilinogen are generally given as 50 to 250 mg., which means that the recovery of bile pigment in the stool may be 20 to 100 per cent of the actual production. It is not known what happens to the lost pigment but it is suspected that much of it is converted to compounds such as dipyrroles that do not give color with the aldehyde reagent.

The concentration of bilirubin in normal plasma does not vary to any considerable extent from day to day, because the pigment is removed from the plasma as fast as it enters. To determine the length or time that bilirubin remains in the plasma we apply the formula M = PL as already indicated. When the plasma volume is 3,000 ml. and the concentration of bilirubin is 0.5 mg. per 100 ml., the total quantity of bilirubin in plasma (M) is 15 mg. P is the 250 mg. of bilirubin that are produced each day. Then L, the average time that a bilirubin molecule remains in the plasma, is 0.06 days or approximately one and one-half hours. This is a rather long time and it suggests that no great proportion of the bilirubin is cleared from the plasma during a single trip through the liver. These calculations are valid only if it is assumed that all bilirubin produced in the reticulo-endothelial system is transported in the plasma. If some bilirubin is formed in the liver and excreted directly into the bowel, the average survival of bilirubin in the plasma would be greater than one and one-half hours.

BILE PIGMENTS IN HEMOLYTIC DISEASE

In chronic hemolytic anemia with stimulation of the bone marrow to its fullest erythropoietic effort the production of hemoglobin proceeds at about six to eight times the normal rate. Since the normal rate of production of useful hemoglobin is 6 or 7 gm. per day, the output in this sort of hemolytic disease would be 35 to 45 gm. per day. When the level of anemia in the patient does not fluctuate, the destruction of hemoglobin must equal production and therefore the amount of bilirubin produced each day remains constant and proportional to the production of hemoglobin. If 35 mg. of bilirubin are derived from each gram of degraded hemoglobin, the anticipated production of bile pigment from hemolyzed red cells in these patients is 1,200 to 1,600 mg. per day. This does not take into account the "early appearing urobilinogen," previously discussed, which constitutes 10 to 20 per cent of the total urobilinogen excreted in normal subjects. Because of the short survival of red cells in hemolytic anemia much of the urobilinogen derived from the circulating hemoglobin appears in the feces during this early period, making it impossible to identify urobilinogen that might have been derived from sources other than circulating red cells. If it is assumed that the "early appearing urobilinogen" is geared to hemoglobin synthesis—and this seems a reasonable assumption—we must add 10 or 20 per cent to the daily bile pigment production. If the anticipated output of the normal 70 kg. subject, computed in this fashion, is approximately 250 mg., in hemolytic disease in which the output is six or eight times the normal the anticipated daily production of bile pigment would be 1,500 to 2,000 mg.

The amount of bile pigment that can actually be recovered from the feces of such a patient is usually short of the anticipated amount. Measurements of fecal urobilinogen may range from 500 to 1,500. In one patient with hereditary non-spherocytic anemia whose fecal urobilinogen was measured each day for two months the four-day averages varied from 400 to 2,000 mg. per day. (The anticipated value calculated as

indicated was 1,800 mg.) Furthermore, it was found that the changes occurred in a cyclic fashion, moving from the high to the low extremes in what appeared to be a twenty-five-day cycle. The intensity of the patient's hemolytic disease did not vary during this period.[4] A similar study in a patient with nocturnal hemoglobinuria, whose disease was stabilized and not given to crises, showed that the daily output of urobilinogen varied from 90 mg. to 340 mg. per day.[1] The anticipated output was about 500 mg. per day. The change from one extreme to another was gradual but no regular cycle was apparent.

The reason for the variability of fecal urobilinogen is not known. The deficit of pigment in the stool may be due to the degradation of tetrapyrrolic urobilinogen to dipyrroles.

Hemolytic Index. From time to time it has been proposed that the severity of hemolytic disease might be accurately measured by relating the fecal urobilinogen to the amount of hemoglobin in the body. It was found empirically that normal adult subjects excrete 10 to 20 mg. of urobilinogen per day for each 100 gm. of circulating hemoglobin.[17] (One can calculate that they should excrete 30 to 35 mg. per day if all of the bile pigment could be recovered as urobilinogen.) From the great variability of urobilinogen excretion in patients with chronic stabilized hemolytic disease it can be seen that the hemolytic index would also show great variability and therefore does not provide a consistent index of the severity of hemolysis.

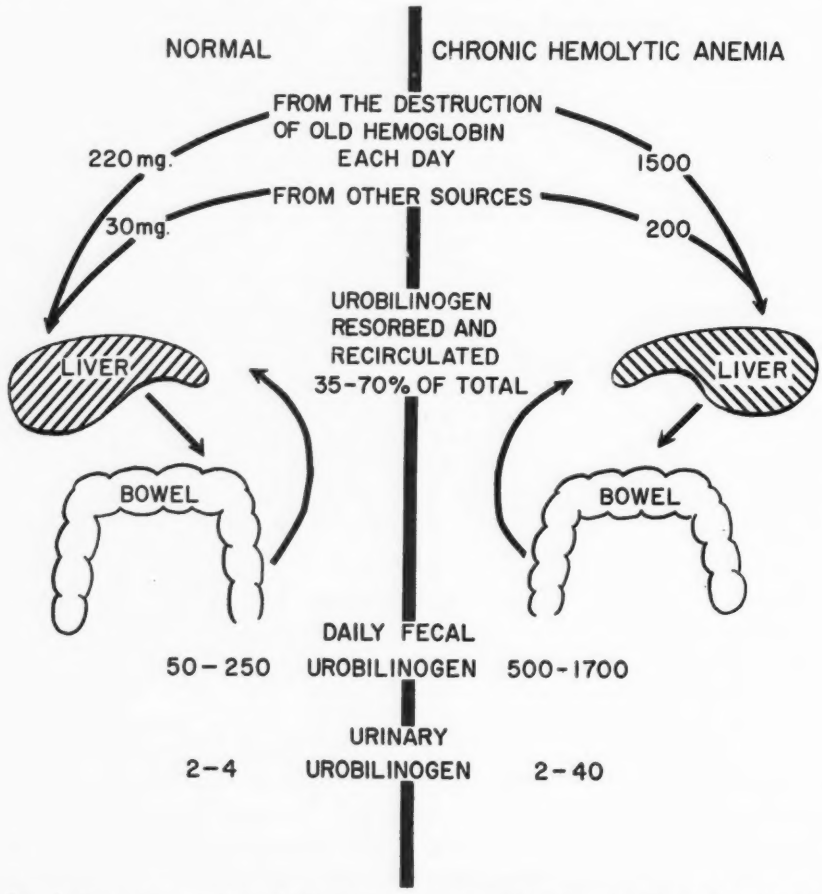

FIG. 3. Normal excretion of bile pigment contrasted with excretion in hemolytic disease. The appearance of situs inversus on the right may be ignored; the patient is viewed from the rear. Urinary urobilinogen is derived from the recirculated pigment.

When it is desired to measure fecal urobilinogen, it should be recognized that certain conditions may artificially reduce it. Values tend to be low in constipated people. In severe diarrhea bilirubin may pass through the bowel unaltered, as it does in the newborn with no bacteria in the colon and in patients receiving antibiotics that suppress the growth of intestinal bacteria.

Bilirubin, of course, does not react as urobilinogen with Ehrlich's aldehyde reagent. To establish the average daily excretion of urobilinogen it has been recommended that all feces be collected on at least four consecutive days. The measurement of fecal urobilinogen was once the most reliable instrument for the diagnosis of hemolytic anemia. Recently, and especially since the advent of radioactivè chromium, the determination of red cell life span has provided a more sensitive and reliable diagnostic method.

Urinary urobilinogen comes from the portion of fecal urobilinogen that is resorbed in the colon and recirculated. (Fig. 3.) In the normal urine less than 4 mg. are excreted in twenty-four hours. The amount is increased when the excretory function of the liver is impaired and it may also be increased in hemolytic disease when the amount of recirculated urobilinogen is great. But the urinary urobilinogen is not always abnormal in patients with hemolytic anemia and the presence or absence of large amounts cannot be relied upon in the diagnosis of hemolytic disease.[25] In one patient with hereditary nonspherocytic hemolytic anemia studied for fifteen consecutive days the urinary urobilinogen was found to vary inversely with the amount in the feces.[4] This variation in urinary urobilinogen is as obscure as the variation in fecal urobilinogen discussed previously.

PLASMA PIGMENTS IN HEMOLYTIC DISEASE

Bilirubinemia is the term used to designate the presence in the plasma of bilirubin in excess of the upper limits of the normal concentration. This figure is generally accepted to be 0.8 mg. per 100 ml. but the normal is often lower than this, about 0.5 mg. In chronic hemolytic anemias, such as hereditary spherocytosis and sickle cell anemia, the concentration of bilirubin is usually about 3 to 4 mg. If the formula M = PL is applied to this situation, it is found that 105 = 1750 L, where the plasma volume is 3,000 ml., the concentration of bilirubin is 3.5 mg. per 100 ml. and the daily production of bilirubin is 1,750. Thus L, the average life span of a bilirubin molecule in the circulation, is about one and one-half hours which is the same figure that was derived for L in the normal situation. This indicates that *the rate of bilirubin clearance in chronic hemolytic jaundice is normal* and that the bilirubinemia is due and is proportional to the augmented amount of pigment that must be cleared.

Higher plasma concentrations of bilirubin are sometimes encountered in hemolytic disease. There are a few cases on record in which values were found between 10 and 15 mg. but these are rare.[12] A lesser degree of hyperbilirubinemia (5 to 10 mg.) may occur during hemolytic crises when pigment production is temporarily increased. It may also occur when pigment excretion is interfered with. The latter may result from incapacity of the liver with a decreased rate of clearance or from obstruction of the bile ducts with "regurgitation" of bilirubin into the plasma. Gallstones which may obstruct the ducts are a common complication of chronic hemolytic disease. It should be recognized that increased hemolysis and impairment of the liver's excretory function may coexist.

The bilirubin in hemolytic disease is often referred to as "protein-bound" or "indirect" bilirubin. "Direct" bilirubin is encountered in biliary obstruction and hepatitis; it is believed to be bilirubin that has been excreted into the biliary canaliculi and has then been regurgitated into the plasma. Until recently it was thought that direct bilirubin was not bound to plasma protein. However, electrophoretic studies have shown that all plasma bilirubin, both "direct" and "indirect," move with the albumin and alpha-globulin fractions of plasma protein and therefore are presumably "protein-bound."[12] The terms "direct" and "indirect" refer to the behavior of the pigments in the van den Bergh reaction. The "direct" bilirubin produces an immediate development of color with Ehrlich's diazo reagent whereas the "indirect" bilirubin does not produce color until alcohol has been added, presumably to split the pigment-protein bond. It would seem that the "indirect" bilirubin is more firmly fixed than the "direct." This may account for another phenomenon associated with these two types of bilirubinemia. When "direct" bilirubin is present in the plasma —either alone or together with "indirect"— bilirubin is excreted into the urine, for the kidney is somehow able to release it from the protein bond. "Indirect" bilirubin, even when present in high concentration, does not cause bilirubinuria.[11] Hence the jaundice associated with hemolytic anemia has in the past been called "acholuric jaundice."

During crises of hemolytic disease the plasma bilirubin concentration may vary. During severe hemolytic crises the destruction of hemoglobin is rapidly accelerated and the patient's

jaundice darkens. During aregenerative crises, when increased anemia results from a failure of the marrow to produce red cells, the bilirubin of the plasma may fall though hemolysis continues.[18] It has been observed clinically that the jaundice of patients with hereditary spherocytosis may lighten during febrile illnesses even though the hemolytic process appears otherwise unchanged.[27] Because the plasma bilirubin may be normal in hemolytic disease, the presence or absence of jaundice is not a reliable criterion for establishing the diagnosis.

Hemoglobinemia describes the presence of extracorpuscular circulating hemoglobin in excess of the normal concentration. The upper limit of "hemochromogens"—substances that react to give a color with benzidine—in normal plasma is generally accepted to be 5 mg. per 100 ml., but when blood is carefully drawn and centrifuged the concentration is rarely in excess of 3 mg.[5] The presence of hemoglobinemia is evidence of intravascular hemolysis of red cells. Its presence may be regarded as prima facie evidence of hemolytic disease, but it is not always present. The plasma hemoglobin is normal, for example, in hereditary spherocytosis, hereditary non-spherocytic hemolytic anemia, thalassanemia minor and in the less severe cases of autoimmune hemolytic anemia. It may be slightly elevated in hemoglobin-C disease and in sickle-cell thalassanemia disease. It is usually moderately elevated (10 to 25 mg.) in sickle-cell anemia, Cooley's anemia, sickle-cell-hemoglobin-C disease, and severe autoimmune hemolytic anemia.[3] High levels of plasma hemoglobin are encountered in the diseases in which hemoglobinuria occurs, for hemoglobinuria indicates a plasma concentration in excess of the renal threshold (70 to 140 mg.). During hemolytic crises in any hemolytic disease, the plasma hemoglobin may become increased. Hemoglobinuria has been known to occur even in hereditary spherocytosis and sickle-cell anemia.[5]

Hemoglobin released by intravascular hemolysis is handled in several ways. (Fig. 4.) Most of it is probably taken up by the reticulo-endothelial system and degraded in the same way as the hemoglobin of red cells ingested by phagocytes. Some of the pigment may be lost as hemoglobin in the urine. A third channel for elimination of plasma hemoglobin is its conversion to methemalbumin.[8] The rate of clearance of methemalbumin from the plasma appears to be slower than that of hemoglobin when both are present together. In one subject in whom the total concentration of hemochromogens was 450 mg. and that of methemalbumin was 45 mg. per 100 ml., the half-life of total hemochromogens was 135 minutes and that of methemalbumin was 350 minutes.[3] Methemalbumin does not appear in the urine during hemoglobinuria even though present in plasma concentrations as high as 50 mg. per 100 ml. It is not known if there is a renal threshold for this pigment, but albumin itself is not ordinarily lost in the urine.

It requires little free hemoglobin to produce hemoglobinemia. For example, if the red cells in 10 ml. of normal blood were abruptly hemolized intravascularly, the hemoglobin released would raise the plasma level of an average sized man by 50 mg. per 100 ml. This seems a trivial amount of hemolysis to produce such a degree of hemoglobinemia, but to *maintain* the plasma hemoglobin at that level would require the release of about 30 gm. of hemoglobin per twenty-four hours, almost five times the normal daily production.* The amount of intravascular hemolysis required to maintain even moderate degrees of hemoglobinemia is not insignificant.

In most diseases characterized by hemoglobinemia it can be ascertained that more than one hemolytic mechanism is at work. For example, in sickle-cell anemia the plasma hemoglobin level is usually around 20 mg. yet the cells of the reticulo-endothelial system demonstrate notable erythrophagocytosis; we estimate that approximately one-third of the hemolysis is intravascular and the rest is intracellular. In Cooley's anemia about one-half of the hemolysis is intravascular. In nocturnal hemoglobinuria most if not all hemolysis appears to be intravascular. In hereditary spherocytosis, on the other hand, almost all hemolysis is intracellular, and most of it occurs in the spleen.

Role of the Kidney in Hemoglobin Breakdown.[29] The proportion of plasma hemoglobin that is lost into the urine depends upon the concentration in the plasma. Hemoglobinemia was artificially induced in a normal subject whose renal threshold was about 75 mg. of hemoglobin per 100 ml. of plasma. In one trial a concentration of 465 mg.

* This calculation is based upon the half-life of plasma hemoglobin in normal men. At plasma concentrations of 50 mg. per 100 ml. and less, the half-life of hemoglobin released by the injection of distilled water is about forty minutes. It is longer at higher concentrations.[3] In patients with chronic hemolytic anemia the mechanism for clearance of plasma hemoglobin has been found to be more efficient than normal.[22]

was achieved; approximately one-third of this hemoglobin was recovered in the urine. In a second trial several months later a plasma concentration of 110 mg. of hemoglobin was achieved, and approximately one-tenth of the hemoglobin was found in the urine.[3]

of plasma hemoglobin is low, but much iron may be lost in the urine when hemoglobinemia is intense. Amounts of iron representing 2 to 5 gm. of hemoglobin have been recovered in one day's urine of patients with nocturnal hemoglobinuria.[6] Hemosiderin is not found in normal

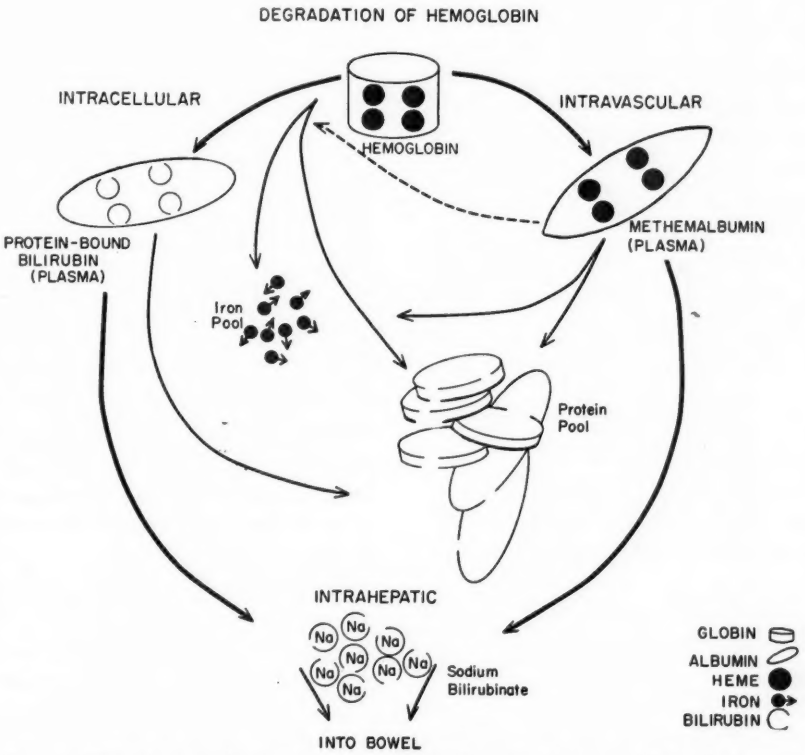

FIG. 4. The plasma pigments in hemolytic disease. Abnormal hemolysis may occur in the phagocytes of the reticuloendothelial system or in the plasma of the circulating blood. In the phagocytes the porphyrin of the hemoglobin is degraded to bilirubin, which is then bound to plasma protein and carried to the liver where it is excreted. Hemoglobin released into the plasma may also be taken up by the reticuloendothelial cells or, if the concentration is great enough, it may be excreted in the urine causing hemoglobinuria. Some of the plasma hemoglobin undergoes oxidation to form methemoglobin. In human plasma this pigment does not last. The heme groups become detached and fasten themselves to molecules of plasma albumin forming methemalbumin. This pigment is probably removed from the plasma by the liver and other organs of the reticuloendothelial system and degraded to bilirubin. In both channels of hemoglobin degradation the iron and protein are salvaged and used again.

The kidney acts as an organ for clearance of hemoglobin whether or not hemoglobinuria occurs. Even with low grade hemoglobinemia, hemoglobin is present in the glomerular filtrate but it is removed and degraded by the tubular epithelium without appearing in the urine. In such cases some of the hemoglobin iron finds its way into the urine where it may be detected as hemosiderin. Chronic hemoglobinemia is almost always associated with hemosiderinuria.[5] The amount may be microscopic when the level

urine. Since the kidney can strip iron from hemoglobin it is probable that the renal epithelium also is capable of acting as a reticulo-endothelial organ to produce bilirubin from the porphyrin, but this has not been demonstrated.

The kidney is not the major organ for degradation of plasma hemoglobin. Experiments in rats showed that with or without kidneys injected hemoglobin disappeared from the plasma within the same period of time. Before the kidneys were removed the clearance was an

exponential function; without the kidneys it was linear. Not all of the difference could be accounted for by the hemoglobin in the urine.[9] This suggests that the kidney plays a greater role in clearance of the plasma when the concentration of hemoglobin is high.

SUMMARY

1. The production of hemoglobin in normal humans is about 90 mg. per kg. of body weight per day, and an equal amount of hemoglobin is destroyed each day. The life span of hemoglobin is the same as that of red cells, about 120 days. The bile pigments derived from the hemoglobin of worn-out red cells and other sources amounts to about 250 mg. per day in a 70 kg. man. The mechanisms of formation and degradation of hemoglobin and the fate of bile pigments are discussed.

2. In hemolytic anemia the production and destruction of hemoglobin may be six or eight times the normal rate if the response of the bone marrow is not hampered. The production of bile pigment is proportionately increased above the normal.

3. The rate at which bile pigment is cleared from the plasma is the same in patients with uncomplicated hemolytic jaundice as it is in normal subjects. In both cases the life span of bilirubin molecules in the plasma is approximately ninety minutes.

4. When hemolysis occurs in the plasma, causing hemoglobinemia, the hemoglobin may be degraded by different mechanisms than those involved when hemolysis occurs in phagocytic cells. The clearance and degradation of plasma hemoglobin are discussed.

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Combined Staff Clinic

Pituitary-Gonadal Relationships

THESE are stenotyped reports of Combined Staff Clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Gilbert H. Mudge.

DR. JOSEPH W. JAILER: Although the gonadotrophic hormones were investigated earlier than the other pituitary hormones, at the present time we probably know less about them than any of the others. They have less clinical value than such pituitary hormones as ACTH or TSH, the thyrotrophic hormone, since stimulation of the adrenal or the thyroid can be accomplished with ACTH and TSH, respectively, whereas the available pituitary gonadotrophins exert no such effects on the gonads. The reason for this may be that the gonadotrophins are not as well defined; or the failure may be something inherent in the target organ, namely, the ovary or the testis. Suffice it to say that at the present time there are no good pituitary gonadotrophic hormone preparations available for human use.

Our ignorance in this field is so great that we are not even sure of the number of gonadotrophins present. We now think in terms of two or three, but there was a time when five different pituitary gonadotrophins were postulated. One was called the antagonist; another was a synergist; and a third was called an ovulating hormone. These hormones have met their deserved fate.

The first of the three presently recognized gonadotrophins is the follicle-stimulating hormone, or FSH. This substance stimulates spermatogenesis in the male rat and causes growth of ovarian follicles in the female rat.

The luteinizing hormone, LH, also called the interstitial-cell-stimulating hormone, ICSH, stimulates the Leydig cells in the testes of the male and causes further ovarian stimulation in the female. It is thought that this hormone, along with the follicle-stimulating hormone, causes ovulation.

The third gonadotrophic hormone is luteotrophin, or prolactin. Aside from its effects upon milk production, it supposedly prolongs the life of the corpus luteum and stimulates it to secrete progesterone. Apparently, it has no function at all in the male. It should be pointed out that the evidence for the action of luteotrophin comes from studies on rodents. This mechanism probably exists in the rat but, as often happens, one cannot transfer these results directly to man. There have been some recent reports that show that the life of the corpus luteum in the normal woman cannot be prolonged by the administration of large doses of luteotrophin whereas it can be prolonged by a pituitary-like hormone—chorionic gonadotrophin—which, of course, is of placental and not of pituitary origin. This chorionic gonadotrophic hormone is, as you know, very similar in its biologic effects to the pituitary hormone, LH or ICSH. Consequently, it must be stated that the final answer to the role of luteotrophin is not available at the present time.

From this short introduction to the gonadotrophic hormones of the pituitary, we should like to proceed to a consideration of some of the aspects of hypogonadism in the male, which Dr. Werner will discuss.

DR. SIDNEY C. WERNER: The problem of testicular failure in the male can be approached from several points of view. One can consider the problems involved according to the age period of the patient: difficulties originating before the onset of puberty and interfering with subsequent development, or gonadal failure developing at the time of puberty with arrest of development at this stage, or failure subsequent to the completion of normal maturation. This approach was outlined in an article appearing in the July, 1947, issue of the *American Journal of Medicine*, and one can find there the many causes of interference with gonadal function at these different times of life.

About three years later, however, a more physiologic approach was presented from Dr.

Albright's laboratory in Boston. For many years these workers collected biopsy material from the testes of men with various testicular defects, and they concomitantly determined the urinary excretion of follicle-stimulating hormone and 17-ketosteroids. This integrated study, which can be recommended highly, appeared in the *Journal of Clinical Endocrinology*, vol. 11, page 121, 1950.

On the basis of their findings, and of a previous paper originating from that laboratory by Dr. Klinefelter which described a syndrome of failure of function of the tubules of the testis associated with a high FSH urinary output, Dr. Howard and co-workers proposed a new concept of the hormonal regulation of the internal secretory and the spermatogenic functions of the testis.

To review briefly the classification of the 120 patients in this series, the criterion for grouping was the content of gonadotrophin in the urine. Whether this gonadotrophin is truly a follicle-stimulating hormone, such as has been postulated in the female, or whether this hormone is in effect a mixture of follicle-stimulating hormone and luteinizing hormone, is discussed in the article cited. The authors conclude that if there is a luteinizing hormone, it is unimportant in appraisal of the assay values. Thus the patients could be classified in terms of disorders with low follicle-stimulating hormone output, normal FSH output, or high FSH output.

All or virtually all so-called eunuchoid males (males who fail to enter puberty or enter puberty to a very limited extent) fall into the group with low FSH. It is interesting to note that about two of every three patients with the Klinefelter syndrome, in whom there is a primary disturbance in the tubules, were not eunuchoid and only one of three was called distinctly eunuchoid.

The second group, with low FSH output, are, as might be expected, those patients in whom the defect arises because of destruction of the anterior pituitary. In some of this group the defect was iatrogenic, the result of estrogenic therapy which, because of the reciprocal relationship between gonad and pituitary, results in atrophy of the testis because of suppression of gonadotrophin output.

We shall not discuss in detail the conditions with normal FSH. These primarily concern spermatogenesis and present problems more suitable for a discussion of sterility.

The last group is characterized by a high excretion of FSH. In congenital aplasias of the testis there is a high FSH output, very similar to that which follows castration. Then there is the Klinefelter syndrome, which histologically is characterized by a sclerosing degeneration of the tubules; the tubules show varying stages of atrophy and a thick hyaline membrane, indicating some sort of sclerotic process. As I said before, two of three such patients complain not of eunuchoidism but of sterility, and exhibit either azoospermia or oligozoospermia.

Last in this group is the male climacterium or male menopause, the very existence of which has been a matter of dispute. In a recent review of the whole situation it appeared to me that there was evidence that in rare instances true gonadal failure, consistent with such a disorder, may occur in the older male. The disorder can be demonstrated in part by testicular atrophy, in part by high FSH output in the urine, but it is interesting to note that in reports from twenty leading laboratories in this country there was no uniformity of opinion as to either the nature of the histologic change in the testes or the constancy of an increased output of follicle-stimulating hormone in the urine. The disorder undoubtedly exists, and can be improved by proper therapy, but one must be very skeptical of the diagnosis in many instances.

The testis, as you will recall, is composed of tubules, of large triangular cells termed the Leydig cells, and of rather thin cells placed between the gametocytes, the Sertoli cells. The obvious function of the gametocytes is to produce sperm. The Leydig cells are recognized as the site of androgen production by the testis. The Sertoli cells have been thought by some to have a nutritive function for the gametocytes. In Dr. Albright's clinic they consider the sustentacular or Sertoli cell to be the site of elaboration of a substance analogous to estrogen, if not indeed an estrogen, and that from failure of this cell originates many of the clinical defects which have just been outlined.

I should like to comment on the functions of this so-called "X" hormone of the sustentacular cells of the testis, as postulated by Dr. Albright. First, the Sertoli cells, or more specifically the "X" hormone, seems to promote spermatogenesis; when this substance is missing, spermatogenesis seems to be concurrently impaired. Whether this is a cause and effect relationship, however, is not established.

Second, the Albright school believes that the

"X" hormone inhibits excessive release of follicle-stimulating hormone by the pituitary, such as occurs for example in castration, as opposed to eunuchoidism. When one gives androgens to a castrate, or to a man with the Klinefelter syndrome, the titer of follicle-stimulating hormone does not decrease until very large doses of androgen are employed; whereas if small doses of estrogen are given, there is an almost immediate lowering of output.

The other action of the "X" hormone which is postulated is that it stimulates the pituitary to release luteinizing hormone which then exerts possible effects upon the tubules.

Finally, since in Klinefelter's syndrome a significant number of patients develop gynecomastia, Dr. Albright's group speculate as to whether the "X" hormone has an effect in inhibiting the formation of gynecomastia.

Dr. McCullagh, who really was responsible for the first isolation of such a substance, perhaps the "X" substance itself, gave it the name of inhibin, back in 1932 or 1933. He found the material in aqueous extracts of bull testis, and noted that the effects of its injection were analogous to those of an estrogen. He speculated as to whether this material was, in effect, either an estrogen or Δ^5-pregnenolone. He has recently described a syndrome in which the Leydig cells of the testis are missing but in which there is adequate spermatogenesis and a normal FSH output. That would tend, in part, to fit with the concept of the Boston school.

On the other hand, Maddock and Nelson have performed a very interesting experiment which gave results diametrically opposed to the theory that the Sertoli cell is the site of inhibin or estrogen production. They gave very large doses of chorionic gonadotrophin to healthy men. Then they biopsied the testis after about two months. They found basement membrane hyalinization, strictly comparable to that encountered in the Klinefelter syndrome, together with azoospermia and very marked hypertrophy of the Leydig cells, but no changes at all in the Sertoli cells, or at most merely the changes which one finds with inactivity. They noted gynecomastia in a significant number of patients. Moreover, the 17-ketosteroid output was doubled, but the estrogen output of these men was sharply increased.

Since it is possible that the adrenal might have been the source of this estrogen output, they treated several women with Addison's disease and found no increase in output of estrogen. They treated several castrates and again found no increased output of estrogen. Therefore, the evidence strongly indicates that, although estrogen is being elaborated in the testis, from the histologic appearance the steroid does not originate in the Sertoli cells but in the Leydig cells.

Now, the clinical picture. First, as an example of eunuchoidism, we may consider a patient who, when first seen, was twenty-three years old but who had the general appearance of a sixteen year old boy. There was no axillary or pubic hair, although he did have a little development of his genitalia. His testes were about 0.8 cm. to 1 cm. in diameter. Prior to his visit here he had received eight months of vigorous chorionic gonadotrophic therapy, without much change. His muscles were very thin. The urinary output of follicle-stimulating hormone was so meager that the titer could not be determined on repeated assay. His urinary 17-ketosteroid excretion was about 5 mg. in twenty-four hours.

Six years later, on testosterone replacement therapy, his condition had changed remarkably. He had grown 7 inches (this from the age of twenty-three to twenty-nine) and had gained 70 pounds. He is now the father of two children, and Dr. Scudder has been able to establish by means of blood groups of mother, father and children, that he really is the parent of these children. Over the nine years of testosterone therapy he developed a marked increase in the size of his gonads and biopsy revealed normal spermatogenesis in one testis, with sperm counts of 13 million per cc. (The sperm counts had been zero for many years.)

Eunuchoidism is characterized not only by the local changes of testosterone–lack but also by peripheral changes such as failure of normal male muscle development. The impetus to growth, or the growth spurt, occurred in this patient at the age of twenty-three years; the epiphyses were still open as they usually are in these people. Thus, as Dr. Allan Kenyon showed many years ago, testosterone causes nitrogen and deposit protein to be retained in significant places in the body. The skin shows very striking changes with treatment; and the oily seborrhea, the result of activity of the sebaceous glands of the adult and puberal male, is reproduced upon the appearance of testosterone in the circulation. The blood count also is influenced. As you know, the child has a blood count somewhat lower

than that of the adult, and adult females have a blood count normally lower than that of the adult male. The eunuchoid patient treated with testosterone shows a shift to the adult male blood picture, with an increase in hemoglobin and in the blood count.

The diagnosis of eunuchoidism can be confirmed in the laboratory, although it is obvious clinically in most instances. Testicular biopsy is the most decisive laboratory procedure. The output of follicle-stimulating hormone is important in separating out the Klinefelter group. The output of interstitial cell hormone has been measured by Dr. McCullagh and his group; and if that can really be done reliably, it may be important in classifying these patients. The urinary output of 17-ketosteroids may be low or normal and is not particularly helpful. Determination of the output of estrogens is not reliable, and not particularly helpful.

The next patient is a boy who appeared to be about twelve but was really sixteen. From the age of twelve to sixteen he was here at the hospital, undergoing vigorous therapy for non-tropical sprue, and grew only an inch. He was infantile; obviously prepuberal, but not a eunuchoid. He was a eunuch because his testes apparently never developed due to congenital aplasia. The output of follicle-stimulating hormone was high. Despite his non-tropical sprue, he put on 80 pounds as a result of testosterone therapy, he grew about 8 inches, and is now working. He is carrying on a very active and vigorous life, is married and, although he will not have children, he is very happily married. The effectiveness of this therapy is quite obvious.

I would like, however, to differentiate this group from the so-called Fröhlich's syndrome, which is usually a wrong diagnosis made in normal but obese boys before puberty. This is in contrast to the true Fröhlich's syndrome patient, as exemplified by Fröhlich's original patient, who hardly looked like the obese boy just described. Fröhlich described a boy with a pituitary carcinoma invading the sella and arrested development in early puberty—an entirely different type of problem.

I shall close with some remarks about the male climacterium, because I believe that this syndrome does exist and has received scant attention in many clinics. It is classically described as a syndrome similar to the female menopause, characterized by onset of vasomotor symptoms, weakness, loss of libido and emotional upset. However, such a clearcut picture is unusual, and one is much more apt to find waning potentia and waning libido in a person who is, in some instances, seemingly quite well adjusted to life and has carried on a normal existence. Such a story should raise suspicion of this disorder, especially if accompanied by evidence of testicular atrophy. On the other hand, one has to differentiate the patient with an emotional problem and one has to be at least sensible about age of onset. The male climacterium has been reported with onset as early as age twenty-six. If one reads such histories very carefully, one finds that with a six- or seven-year history of symptoms leading to the "climacterium" at age twenty-six, the onset was in the middle of puberty, which is a little strange, to say the least.

I want to cite two patients to illustrate the points I am making. One was a Texas rancher, a very healthy, vigorous man in his later fifty's who decided to take a young bride. He was a little concerned about being somewhat too old for this young bride. After a year of perfectly happy marriage they had an altercation, with several episodes of rather unfortunate emotional outbursts, whereupon he exhibited indications of the male climacterium. It was not until this situation was explained and he was assured that he was physically well that his "climacterium" disappeared and he reentered normal adult manhood.

The other patient, on the other hand, was a tense, rather nervous man who had fled Germany to France, had become affiliated with one of the large American companies there, worked under great tension, and very gradually noticed that he was less and less interested in sexual matters. He was concerned. He became quite moody and introspective about it. He appeared in this country on one of the trips sponsored by his company and sought medical aid. It was apparent that this man did have slight but real testicular atrophy, with no other systemic difficulties, and his twenty-four-hour output of follicle-stimulating hormone exceeded 80 mouse units. With testosterone therapy, he became apparently perfectly normal again within a space of less than one month, and has continued to be very happy and active. One must therefore use a certain amount of clinical discretion in making the diagnosis of male menopause.

DR. JAILER: Not only is there dispute as to the nature of the gonadotrophins but we do not know what factors initiate their secretion. Apparently, the gonadotrophic complex lies dormant during childhood and sometime during adolescence secretion begins. This causes gonad onset of the first menstrual period; in the male, it is difficult to ascertain exactly when puberty occurs.

Sexual precocities in children may occur along isosexual lines (that is, characteristics of the individual's own sex emerge) or develop-

TABLE 1*

CAUSES AND TYPES OF SEXUAL ABNORMALITIES

Site of Origin	Age of Onset	Sex	Type of Sexual Abnormality	Pathology	17-keto-steroids
I. *Hypothalamus*	Prepuberal	M>F	Isosexual	Tumor or inflammatory	N or +
II. *Constitutional precocious puberty*	Prepuberal	Mostly F	Isosexual	?	N or +
Albright's syndrome	Prepuberal	Mostly F	Isosexual	?	N or +
III. *Gonads*					
A. Ovary:					
(1) Arrhenoblastoma	Adult	F	Heterosexual	Tumor	N or +
(2) Hilus cell	Adult	F	Heterosexual	Tumor	N or +
(3) Granulosa cell	Adult or prepuberal	F	Isosexual	Tumor	N
B. Testes					
(1) Leydig cell tumor	Prepuberal	M	Isosexual	Tumor	N or ++
IV. *Adrenal cortex*					
A	Congenital	M	Isosexual	Hyperplasia	++++
	Congenital	F	Pseudoherma-phrodite	Hyperplasia	++++
B	Prepuberal	M	Isosexual	Tumor or hyperplasia	++++
	Prepuberal	F	Virilism	Tumor or hyperplasia	++++
C	Adult	F	Virilism	Tumor or hyperplasia	+→++++
		F or M	With Cushing's syndrome	Tumor or hyperplasia	0→ ++++

* Modified from SOFFER, GABRILOVE and JAILER, *Recent Progress in Hormone Research*, 5: 407, 1950.

stimulation and the gradual appearance of puberty.

I should now like to discuss the causes of sexual precocity in children. By definition, puberty occurs between the ages of about eight and sixteen in girls and about eleven to eighteen in boys. No gonadotrophic hormone is found in the urine of children prior to that age. It then gradually appears in the urine in increasing amounts. The hormone is, of course, probably of pituitary origin. It stimulates the gonads, which, in turn, secrete the androgens and estrogens responsible for puberty. In the female, puberty is marked by a definite event, the ment may be so abnormal that it is along heterosexual lines, i.e., virilization of the female and, in very rare cases, feminization of the male.

Table 1 defines the various causes of precocious puberty in children. The first one listed is so-called "hypothalamic precocity." There has been a recent review of this subject in the January, 1954, issue of the *Journal of Clinical Endocrinology*, in which Dr. Bauer reviewed sixty cases of hypothalamic disease, in twenty-four of which precocious puberty occurred. There were nineteen males and five females, and that is the distribution that is found in the older literature as well. Of these twenty-four cases,

nineteen were due to tumor, four to inflammatory disease, and one was due to a degenerative lesion.

It should be emphasized that in the presence of hypothalamic disease sexual precocity is along isosexual lines. The boys tend to grow at an accelerated rate, the penis enlarges, as do the testes. They develop axillary and pubic hair and simulate normal puberty but at a much earlier stage. Gonadotrophin can be detected in the urine; in other words, they excrete FSH titers which are characteristic of adolescence rather than of the chronologic age of the child. The urinary 17-ketosteroids are not particularly elevated, but they vary between 4 to 10 mg. per twenty-four hours. Again, these are values characteristic of adolescence.

The females develop breasts, axillary and pubic hair and may even menstruate. Endocrinologic assays reveal findings similar to those in the male—the presence of urinary gonadotrophin and slightly increased 17-ketosteroids. In addition, estrogens appear in the urine. Vaginal smears show the characteristic cornified cells found in normal women.

Apparently the lesion responsible for this most often involves the posterior portion of the hypothalmus. It should be pointed out, however, that no lesion in experimental animals has been produced in this region, or any region, which causes precocity. The mechanism is obscure. It is claimed by some that the pathologic lesion frees the hypothalamus from cerebral inhibition which, in turn, stimulates the anterior lobe of the pituitary. Others claim that the irritating force of the lesion itself may stimulate the hypothalmus. There is insufficient evidence to establish either theory.

There are other children who present the same endocrinologic picture of isosexual precocity in whom no detectable central nervous system lesion can be found and, since the lesion is unknown, it is called "pituitary" or "constitutional precocity." Again, this is along isosexual lines and, for some reason or other, it is much more common in the female than in the male. Patients with this disorder develop normally, endocrinologically speaking, but they do have many psychiatric problems and difficulties. This applies to the male as well as the female. I should like to emphasize that this type represents true precocity. For example, in boys not only is there evidence of androgen stimulation throughout the body but the testes are stimulated as well. A testicular biopsy from such a patient demonstrates all the stages of spermatogenesis, with mature sperm in the lumen of the tubule. A normal boy's testes reveals only spermatogonia. Parenthetically, this is in contrast to the type of precocious puberty that occurs in adrenal disease, in which the testes are not involved.

In these cases the mechanism which causes the pituitary gland to secrete gonadotrophic hormone at puberty, causes secretion at an earlier age, for some unknown reason, and this leads to "constitutional precocity."

There is a very interesting subclass of constitutional or pituitary precocity which was first described in the Babies Hospital by Dr. McCune and then later amplified by Dr. Albright. It occurs primarily in girls; the isosexual precocity is associated with polyostotic fibrous dysplasia and a very peculiar type of café-au-lait coloration of the skin, usually on the buttocks. The cause is unknown.

A third cause of precocious puberty may lie within the gonad. These are rare. A Leydig-cell tumor, for example, will start secreting testosterone and cause what appears to be isosexual precocious puberty. In reality, however, since spermatogenesis does not occur, we must call this pseudoprecocious puberty.

In the female, granulosa cell tumors of the ovary have been described. These secrete excessive amounts of estrogen and cause feminization. In addition, other types of ovarian tumors have been described, mostly in adults however, which secrete androgens and consequently cause virilization.

The fourth and most common cause of precocity or sexual aberration in children is due to adrenal disease, and this problem has been extensively studied. We shall call this adrenal virilism, because it is primarily a virilizing disease, although we will show that it can also rarely feminize.

The clinical picture depends upon the sex and age of onset. The disease may be present at birth; in other words, it may have its origin during embryologic development. In the female, it produces the so-called "female pseudohermaphrodite." This condition may be so marked that the sex of the child may be undetermined at birth and, as you know, some of these children may actually have their sex mistaken. The infant may be considered by the obstetrician to be a boy with hypospadias, a scrotal urethral

orifice and two scrotal folds and bilateral cryptorchidism. In reality, these patients are girls with an enlarged clitoris and urogenital sinus which bifurcates into both the urethra and vaginal canal. Usually, exploration is necessary to establish the true sex.

So much for the situation at birth. At the age of about a year or so, the child is found to have grown at an accelerated rate, and if x-rays are taken of the bones they show advanced maturation. A child of two may have a bone age of four or six. Very often, these children develop pubic hair and axillary hair, and the clitoris becomes even more enlarged; in other words, these children go on in most instances to virilize.

As for the situation in the male, even though the syndrome begins before birth, *in utero*, it is usually not recognized until much later. The boys appear to be perfectly normal at birth, but at about a year or two of age they begin to grow at an accelerated rate, their bone age is advanced, they develop an enlarged penis, pubic hair, some axillary hair, and even acne. These children are very large during childhood but their epiphyses fuse at an early age so that they end up as short adults.

The condition may occur after birth but before puberty, and then it is usually due to an adrenal tumor rather than to congenital hyperplasia. In the female, of course, virilism is superimposed upon previously normal female genitalia, consequently there is never any difficulty in ascertaining the sex of the patient.

This condition may also begin after puberty. It is much rarer then, but it does occur. In the female, we usually encounter complete virilization, with breast atrophy, amenorrhea, development of hirsutism, muscular development, etc. There have also been described a few cases of feminization of males due to adrenal tumors. These are extremely rare. The tumors can often be shown very easily by means of a presacral aerogram.

So much for the clinical picture of this condition. We should like now to discuss some of the steroidal or endocrinologic manifestations of adrenal virilism. This condition results from the fact that the adrenal glands are in reality factories for the manufacture of steroids.

The most easily determined steroid grouping is the so-called 17-ketosteroids. In adrenal virilism the daily excretion of 17-ketosteroids in the urine is invariably elevated. In Table II are found some characteristic levels for the 17-ketosteroids in this condition. The upper limit of normal in subjects less than eight years of age is about 2 mg./day.

When an adrenal tumor is present the 17-ketosteroids are usually extremely high. However, the height of the 17-ketosteroids does not establish the diagnosis because there is quite an overlap between adrenal hyperplasia and tumor. Generally speaking, but not in all cases, the patients who have an adrenal adenoma excrete large amounts of a beta-ketosteroid, namely, dehydroisoandrosterone in their urine. Also in these children, and especially in those with adrenal hyperplasia, we find increased amounts of pregnanediol which, as you know, is a breakdown product of progesterone. Other steroids, pregnane derivatives such as pregnanetriol, have been found. The latter compound has three hydroxy groups instead of two. Oddly enough, some patients who have become virilized excrete large amounts of estrogens.

You are all familiar with the fact that if cortisone is administered to such patients there is a marked fall in the urinary 17-ketosteroid excretion. At the present time, we have about twenty-five such patients under treatment. Within a short period of time after the administration of cortisone or hydrocortisone the excretion of 17-ketosteroids falls; if adequate amounts are administered, the 17-ketosteroids fall to values which are approximately normal for the age and sex of the individual.

If hydrocortisone is given intravenously over a four-hour period, the 17-ketosteroids fall within four hours and remain depressed for twelve hours, eventually returning to the control values. In a patient with an adrenal tumor no fall in urinary 17-ketosteroids occurs on such a test, nor is there any fall if the cortisone is given intramuscularly.

The mechanism for this appears to be as follows: The pathologic adrenal is secreting large amounts of androgens or androgen-precursors. Now, the androgen can inhibit the pituitary from secreting gonadotrophic hormone, but not ACTH. If cortisone is now given, it inhibits secretion of ACTH and puts the pathologic adrenal "to rest." At the same time, one is supplying a more normal adrenal steroid.

Also, this removes the inhibitor of the gonadotrophic hormone and consequently gonadotrophic hormone would now be secreted. If we follow these female patients for any length of time, especially those in the age group between

ten and seventeen, we find that with continued administration of cortisone these patients very soon develop enlargement of the breasts, they become more feminine, and most of them begin to menstruate. In a few instances we have obtained gonadotrophic hormone titers before whether it be adenoma or carcinoma, administration of cortisone has no effect upon the urinary 17-ketosteroid excretion. We have had experience now with five such tumors, two benign and three carcinoma, and in all cases administration of adequate amounts of cortisone

TABLE II
17-KETOSTEROID VALUES IN PATIENTS WITH "ADRENAL VIRILISM"

Patient	Age (yr.)	Sex	Urinary 17-ketosteroid Excretion (mg./day)	Remarks
			Adrenal Hyperplasia	
A. R.	8/12	F	11.3	Pseudohermaphrodite
T. K.	4	F	26.0	Pseudohermaphrodite
	14		34.2	
C. R.	7	F	42.8	Pseudohermaphrodite
	12		62.4	
B. L.	15/12	F	9.0	Pseudohermaphrodite
C. D.	2½	F	16.5	Pseudohermaphrodite
J. L.	13	F	46.1	Pseudohermaphrodite
K. A.	14	F	46.7	Pseudohermaphrodite
R. E.	10	F	17.2	
R. K.	8	F	19.8	
B. F.	4½	F	9.8	"True hermaphrodite with virilism"
E. B.	5	M	24.8	Macrogenitosoma praecox
	7		28.2	
J. T. T.	6	M	17.4	Macrogenitosoma praecox
W. H.	3¾	M	21.6	Macrogenitosoma praecox
A. R.	9	M	19.2	Macrogenitosoma praecox
S. B.	2½	F	5.5	Pseudohermaphrodite with Addisonian-like symptoms
L. Y.	15/12	M	11.1	Virilism with Addisonian-like symptoms
			Adrenal Adenoma	
F. N.	7	M	175	
			6	After removal
M H.	6½	F	189	
			4	After removal
			Adrenal Carcinoma	
K. C.	42	F	37.8	Mixed syndrome—Cushing and virilism

cortisone, and have shown that, whereas during the control period there was no gonadotrophin in the urine, after treatment with cortisone normal amounts of gonadotrophin were found. We have followed some of these patients for over three years now and, as soon as we stop the cortisone the condition reappears, the 17-ketosteroids bounce right back, the girls who have been menstruating stop menstruating, etc.

An interesting corollary to this response is the fact that if adrenal virilism is due to a tumor, had no effect whatsoever upon the urinary 17-ketosteroids. This would imply that these tumors are independent of pituitary stimulation or control, in contrast to hyperplastic adrenal glands.

For the past two years we have been interested in trying to find out more of what is going on within the hyperplastic adrenals responsible for congenital adrenal virilism. We have been hoping to be able to explain these abnormalities in terms of a steroidal defect, or perhaps even an

inborn error of steroid metabolism. Originally, we attempted to see what happens to these glands if they are further stimulated, and consequently we gave several of these patients exogenous ACTH. When ACTH was given over a period of three days the following were found: (1) as contrasted with normal individuals, there was no fall in the circulating eosinophils; (2) these patients did not retain sodium the way normal individuals did who were stimulated with the same batch of ACTH; and (3) there was no significant increase in the urinary corticoids as measured by the method in use at that time, the so-called formaldehydogenic steroids. Whereas normal individuals, given comparable amounts of ACTH, showed a five- to tenfold increase in the urinary corticoids, the patients with adrenal hyperplasia showed very little increase. Yet the 17-ketosteroids, which were elevated prior to medication, became even higher, and the "pregnanediol complex," which is high in this condition, also rose.

Therefore it would appear that the hypertrophic adrenal glands synthesize hydrocortisone only with difficulty, as indicated by the absence of the three physiologic changes that should have occurred as a result of its secretion. However, the adrenals evidently were capable of elaborating a steroid or steroids which were precursors of both the 17-ketosteroids and the "pregnanediol complex."

Now what steroid or steroids could be precursors of both the "pregnanediol complex" and 17-ketosteroids? It appears that there is such a steroid, namely, a compound called 17-hydroxyprogesterone. This steroid was first isolated from the adrenal glands in 1940 by North and Pfiffner, who showed that it had no progestational activity at all, but that it was androgenic. Through the courtesy of Dr. White, we have had this steroid re-assayed. It was shown that while it was not androgenic when applied locally, when given by mouth it was a fairly good androgen.

We gave 17-hydroxyprogesterone to eight patients and found a rise in the urinary 17-ketosteroids as well as in the so-called "pregnanediol complex." When these urines are separated chromatographically, and the steroids analyzed, the one found in highest concentration is etiocholanolone. Some androsterone also is found, and pregnanediol and pregnanetriol appear to be present. In other words, some of the steroids which are characteristic of adrenal virilism can be obtained by degradation from 17-hydroxyprogesterone. In addition, 11-oxygenated 17-ketosteroids are found in the urine of untreated patients with congenital adrenal hyperplasia. These metabolites could arise from 21-desoxy-hydrocortisone and, indeed, administration of the latter steroid results in the appearance of 11-keto-etiocholanolone, 11-hydroxyandrosterone and other 11-oxygenated steroids.

Pincus, Hechter et al. have demonstrated that surviving adrenal tissue can hydroxylate at the C-11, 17 and 20 positions. Progesterone can be converted to hydrocortisone by such enzymatic action. (Fig. 1.) The normal synthesis of hydrocortisone by the adrenal gland occurs as indicated in Figure 1; and if there is a block in this synthesis, the substances formed prior to the block will pile up and will eventually be secreted. If the block exists at the 17-hydroxyprogesterone level and/or at the level of 21-desoxy-hydrocortisone, these steroids will be secreted and degraded by the body to steroids which may be metabolized to androgens. This will cause the characteristic virilizing manifestations of the disease.

It is suggested that in congenital adrenal hyperplasia there are metabolic blocks which prevent the full synthesis of hydrocortisone, and that some of its precursors consequently pile up. These precursors are then secreted by the adrenal in large amounts and are apparently degraded by the body to androgenic substances, which cause the virilism so characteristic of the disease. (Fig. 2.)

This would tend to lead to a temporary state of hypoadrenalism. However, the pituitary now would secrete excessive amounts of ACTH in order to attain homeostasis; in other words, to stimulate secretion of a normal amount of hydrocortisone. Indeed, it has been shown by Sayers and his collaborators that excessive amounts of ACTH do occur in the blood of patients with congenital adrenal hyperplasia. In order to accomplish secretion of normal amounts of hydrocortisone, excessive amounts of 17-hydroxyprogesterone and 21-desoxyhydrocortisone would be secreted by the gland. If cortisone is given, it inhibits ACTH production, puts this mechanism "at rest," and the progress of the virilism stops.

STUDENT: Do women with pituitary-gonadal precocity have an abnormally early menopause? Have any been followed long enough?

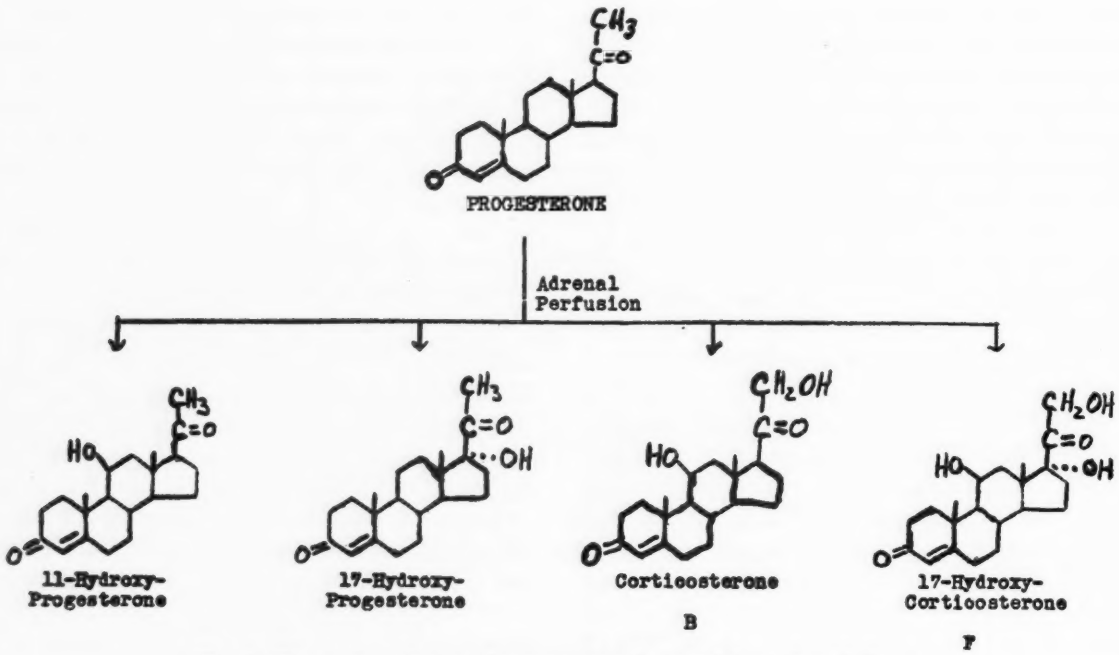

FIG. 1. The hydroxylation of progesterone by surviving adrenal tissue.

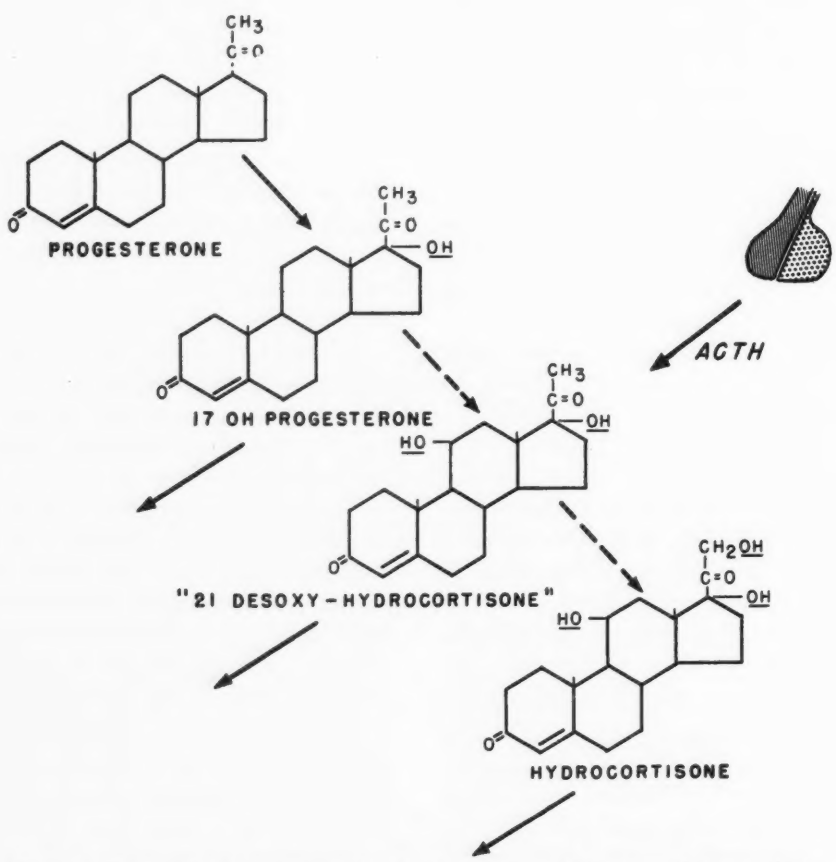

FIG. 2. The postulated enzymatic block in congenital adrenal hyperplasia.

DR. JAILER: I don't know. We have never followed any that long. But we have seen one woman who claims that she started to menstruate at five or six years of age and she was well in her thirties and still having normal menstrual cycles.

DR. D. TAPLEY: Would Dr. Werner describe the therapy which he used to achieve the changes in the eunuchoid male.

DR. WERNER: All the effects described were obtained with testosterone or methyltestosterone, which is preferred because it can be given orally. The dose varies from 20 to about 100 mg. per day of methyltestosterone in different patients.

DR. J. WHITE: How do you account for the increase in testicular size if testosterone is used?

DR. WERNER: That is a very interesting question. There is a certain amount of experimental evidence showing that after hypophysectomy, atrophy of the testicular tubule and loss of spermatogenesis can be prevented by the administration of testosterone or local implantation of testosterone pellets, and that there is preservation of tubule function and spermatogenesis around the pellets. Thus testosterone is probably important in the functioning of the tubule cells.

DR. J. C. TURNER: In the treatment of virilism due to hyperplasia, do you encounter any of the troubles with long-term cortisone administration that are seen in other situations?

DR. JAILER: No, and the reason for that is that one does not have to achieve a so-called "hyperadrenal state" to get an effect. All we are after, actually, is a physiologic inhibition of ACTH secretion, and in some of our patients we can accomplish this with very small amounts of cortisone. In our older girls, the ones who are menstruating, 100 mg. two or three times a week by injection will keep their excretion of 17-ketosteroids close to normal. If the 17-ketosteroids go up, we give them a little more. If we think they are going too low, we give a little less.

DR. C. W. FRANK: Is the administration of cortisone a reliable clinical test for the differentiation of hyperplasia from tumors of the adrenal?

DR. JAILER: Yes. In the past, most of these patients with adrenal virilism were explored with the hope of finding a tumor and removing it. Now, we have had the courage not to explore these patients if they act according to type; for example, we would not explore a young child with virilism who responds to the cortisone test with a fall in the urinary 17-ketosteroids to fairly normal levels and who at the same time has other clinical manifestations typical of adrenal hyperplasia.

DR. IRVING GOLDBERG: You have not mentioned hypo-ovarianism in the female. What is the estrogen used routinely in the treatment of the menopause?

DR. JAILER: In this clinic, estrogens are not used routinely in the treatment of the menopause. Failing ovarian function during the fifth and sixth decade is a normal physiologic event. Many of the so-called menopausal symptoms occur before the menopause or many years after the menses cease. Most women go through this period without untoward symptoms. A study conducted at the Sloane Clinic some time ago demonstrated that in 70 per cent of the women who complained of menopausal symptoms relief was afforded with phenobarbital.

If one is convinced that the symptoms are due to ovarian failure and the usual reassurance and sedation are ineffectual, estrogen may be used. There is no need to use any parenteral preparation. The oral estrogens available, such as stilbestrol and its derivatives, estinyl and premarin are all effective and we use the smallest dose necessary, and give it for the shortest possible period of time. Dr. Taylor has reviewed the entire subject in an excellent article in the *Bulletin of the New York Academy of Medicine*, vol. 29, 1953.

SUMMARY

DR. GILBERT H. MUDGE: The "pituitary-gonadal axis" was reviewed with emphasis on the problems associated with gonadal dysfunction in the male and on various types of sexual precocity. An attempt has been made to interpret the clinical disorders in terms of underlying endocrinologic mechanisms.

The characteristics of the two or three gonadotrophins elaborated by the pituitary are briefly summarized.

Hypogonadism in the male is discussed in relation to several schemes of classification, the most useful of which is based on the urinary excretion of gonadotrophic hormone. The clinical syndromes associated with low, normal or high gonadotrophic output are briefly summarized. The role played by the different types of cells of the testis is reviewed, with particular emphasis on the conflicting evidence regarding the role of the Sertoli cell in the endocrinologic regulation of testicular function. In the presentation of the

clinical varieties of hypogonadism special attention is devoted to the problem of the male climacterium.

The various types of sexual precocity are discussed and classified in terms of the physiologic mechanisms associated with their etiology. The resultant clinical picture depends not only on the etiology and the age of onset but also on whether or not the precocious development is along isosexual or heterosexual lines. Disorders of the adrenal are commonly encountered and the physiology of this gland is reviewed in its relation to gonadal function Evidence is presented that one of the most common disorders, that associated with adrenal hyperplasia, is attributable to a metabolic block in the normal synthesis of adrenal steroids, with resultant accumulation of androgenic steroids. The therapeutic implications of this concept are presented in detail.

Clinico-pathologic Conference

Chills, Fever, Sudden Weight Gain, Oliguria and Arrhythmia

STENOGRAPHIC reports, edited by Albert I. Mendeloff, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, H. F. (No. 231723) a fifty-one year old white businessman, was admitted to the Barnes Hospital on January 21, 1954, with a chief complaint of one week of urinary frequency and nocturia and four days of severe shaking chills associated with diffuse anterior chest pain and fever. He had always enjoyed excellent health until three years prior to admission, when he had an acute myocardial infarction. He was hospitalized elsewhere for one month and then finished his convalescence at home. In general, he did very well following the infarction, his blood pressure ranging between 90 and 120 mm. Hg systolic. A series of electrocardiograms for the next two years had not shown any significant change.

Approximately two months before his admission to Barnes Hospital the patient began to have dyspnea on exertion and episodes of orthopnea, requiring two pillows for sleeping, but suffered no chest pain. About seven or eight days prior to admission the patient stated that he had had some urinary frequency and nocturia; three days later he noted severe shaking chills associated with diffuse anterior chest pain and fever; the pain was accentuated by deep breathing and was accompanied by cough productive of small amounts of blood-tinged sputum. Three days before admission he was given an injection of penicillin, and tetracycline was started. He developed nausea, vomiting and diarrhea; oral antibiotics were discontinued. Chest pain, fever and nocturnal dyspnea persisted, however, and it became necessary for him to sleep upright in a chair. The pain was described as pleuritic, and he specifically denied any similarity of this pain to that he had experienced at the time of his myocardial infarction three years previously. The family had noted that the patient had gained 8 to 10 pounds despite profound anorexia during the week of his illness. Two days prior to admission he developed an herpetic lesion on the upper lip, and some diffuse abdominal pain which was accentuated by lying down. The past history was remarkable chiefly for some symptoms suggestive of arthritis in the past. He had smoked two to three packages of cigarettes daily for many years, but had not smoked at all since his myocardial infarction in 1951. His alcoholic intake had been moderate, and his other habits were not remarkable.

Physical examination revealed the temperature to be 39.6°C., pulse 105, respirations 32 and blood pressure 110/70. The patient was an apprehensive middle-aged male in moderate respiratory distress. Examination of the head was within normal limits. The pupils reacted to light and on accommodation. Fundoscopic examination showed arteriolar narrowing only. Examination of the ears, nose and throat revealed only an herpetic lesion on the upper lip and injection of the soft palate and posterior pharyngeal wall. There were several rather discrete submandibular nodes. The trachea was in the midline. The thyroid was not palpable. There was dullness to percussion at both lung bases and in the right axilla. Breath sounds were bronchovesicular, and rales were heard at both bases. The heart was slightly enlarged to percussion. There was a regular sinus rhythm. A_2 was greater than P_2. No murmurs were heard. One observer believed that there was a gallop rhythm. The abdomen was distended and tympanitic with moderate tenderness on palpation in the right upper quadrant. No organs or masses were palpable. There was a trace of sacral edema. The

extremities were within normal limits. On rectal examination the prostate was enlarged to twice normal size and was mildly tender. Neurologic examination was normal. The laboratory data were as follows: hemoglobin, 12.6 gm.; white blood cell count, 17,400 per cu. mm.; differential count: segmented neutrophils, 82 per cent; stab forms, 1 per cent; lymphocytes, 13 per cent; monocytes, 4 per cent. Red blood cells and platelets appeared normal on the smear. There was moderate toxic granulation of the white blood cells. Urinalysis: specific gravity, quantity not sufficient; pH, 4.5; protein, trace; sugar, negative; centrifuged sediment, numerous coarsely granular and a few finely granular casts, 15 to 30 white blood cells per high power field. Stool: benzidine negative. Cardiolipin: negative. Blood chemistry: non-protein nitrogen, 100 mg. per cent; sugar, 80 mg. per cent. Sputum culture: heavy growth of non-pathogenic yeasts. Blood culture: negative. Roentgenogram of the chest: moderate cardiac enlargement, left ventricular; pulmonary congestion, discoid atelectasis, right lower lobe. Electrocardiogram: anteroseptal myocardial infarction; right bundle branch block, low voltage, semi-horizontal heart position.

The patient was treated with bedrest, a low-salt liquid diet, penicillin 400,000 units intramuscularly every four hours and streptomycin 0.5 gm. every six hours. Within forty-eight hours he became afebrile and felt better except for persistent nausea and vomiting. However, the physical signs within the chest had not changed. His blood pressure had dropped to 90/60, the pulse rate was 90 and the abdomen became more distended and tympanitic. It was also noted that the patient had not voided since the admission urine had been collected. Catheterization of the urinary bladder yielded 300 ml. of amber-colored urine. Specific gravity was 1.010; pH, 5.0; protein, negative; sugar, negative; centrifuged sediment, 1 to 2 granular casts, 8 to 10 white blood cells, 1 to 2 red blood cells per high power field. Urine culture, no growth. Circulation time (decholin®) was twenty seconds; venous pressure, 199 mm. of saline. A Foley catheter was left in place so that the urine output could be followed closely. On the fourth hospital day the non-protein nitrogen had risen to 161 mg. per cent; sodium was 133.9 mEq./L.; potassium, 5.4 mEq./L.; chlorides, 86 mEq./L.; carbon dioxide combining power, 17.6 mEq./L. The electrocardiogram was unchanged. At this time penicillin and streptomycin were discontinued and tetracycline in doses of 250 mg. four times a day was started. The patient was also digitalized because of the elevated venous pressure and circulation time. The oral antibiotic was discontinued when nausea and vomiting persisted and all fluids had to be given intravenously. He remained afebrile but became progressively lethargic and remained oliguric, his urine output ranging between 300 and 800 ml. per day until the eighth day when it rose to 2,250 ml. On this day the patient began to exhibit fine muscle twitchings, but became more alert and appeared to be improving. An electrocardiogram showed auricular fibrillation. The digitalis dosage was increased to toxicity without conversion to normal rhythm. On the ninth day quinidine 0.3 gm. intramuscularly was given every four hours. On the following day the patient reverted to sinus rhythm. During this day it was also noted that the patient had Cheyne-Stokes respiration. On the tenth day he had a gallop at a rate of 100 but with a normal sinus rhythm. Quinidine was then reduced to .2 gm. every six hours. On this regimen bigeminy developed. On the eleventh day the patient's blood pressure dropped to 74/55, the pulse rate to 116, but maintaining a normal sinus rhythm. Nor-epinephrine was added to the intravenous fluids. The patient became more alert, and responded to minor stimuli. On the twelfth day the patient's temperature gradually rose to 38.7°C. At this time his white blood cell count was 50,000 per cu. mm., and later that same day the blood pressure was unobtainable, his respirations became very labored and his heart sounds were absent. The rate of nor-epinephrine administration was increased, artificial respiration was administered, and intracardiac adrenalin was given. In spite of these measures the patient expired on February 2, 1954.

CLINICAL DISCUSSION

DR. VIRGIL SCOTT: This patient was a fifty-one year old businessman with coronary artery disease. Three years prior to his fatal illness he had an electrocardiographically documented myocardial infarction, for which he was treated at another hospital. Following this infarction he did well until two months prior to his entry to Barnes Hospital, at which time he developed symptoms suggestive of left ventricular failure. However, the illness which precipitated his hospitalization apparently began four days prior

to admission with a shaking chill followed by fever. One of the prominent symptoms which was not mentioned in the protocol was the presence of a sore throat at the onset of this febrile episode. During the three or four days of this illness it was noted by his family that he had gained weight in spite of the fact that he was eating practically nothing. The amount of his weight gain was variously estimated to be between 8 and 10 pounds. One observer stated that he had been oliguric from the time of onset of the febrile episode, antedating the sudden chill. On physical examination at the time of entry he was febrile, in moderate respiratory distress, breathing at a rate of 32 per minute. An herpetic lesion was present on the upper lip. There was dullness at both lung bases and in the right axilla and there were rales bilaterally in both bases. The heart was described as enlarged, and there was at one time a gallop rhythm. The blood pressure was 110/70 and it should be noted that he was never in clinical shock at any time while in the hospital, nor is there anything in his history to suggest that he had been in shock at home. The abdomen was distended at the time of admission and remained so throughout his hospital course. There was a trace of sacral edema on admission. His prostate was described as being twice enlarged. Laboratory data showed a relatively normal hemoglobin, a leukocytosis with a left shift, and an acid urine containing a trace of protein and a sediment with many white blood cells, no red blood cells, and many granular casts. No crystalluria was found. He was placed on streptomycin and his temperature became normal in forty-eight hours. Except for the nausea and vomiting he was much improved clinically. The serum non-protein nitrogen which was drawn on the second hospital day was returned on the third hospital day with a value of 100 mg. per cent. At this time the information was obtained that he had not voided since admission and that he probably had had oliguria preceding admission. It was believed then that the patient might have acute renal failure or hypoxic nephrosis. In the ensuing days there was progressive evidence of renal insufficiency, the non-protein nitrogen rising to a maximum of 246 mg. per cent on the eighth hospital day. Meanwhile vomiting and abdominal distention continued. He became lethargic and muscular twitchings were observed. On the seventh hospital day he was seen by a consultant who stated that acute renal failure was probably not present, and suggested that molar sodium chloride be administered. Three hundred ml. of molar sodium chloride were administered on the evening of the seventh hospital day, and an additional 200 ml. in the early morning hours of the eighth hospital day. During the administration of this material the patient improved clinically. He sat up in bed and asked, "What are you doing to me, am I coming to life again"? In the next four hours he put out 400 ml. of urine. In the subsequent discussion we will try to ascertain whether he actually had acute renal failure. By referring to Table 1, the diuresis, if you define diuresis as an output of 400 ml. of urine or more for twenty-four hours, had really begun two days before the administration of molar sodium chloride. On day five he had put out 440 ml., on day six, 595 ml. and on day seven, before the administration of molar sodium chloride, 355 ml. This diuresis then continued, reaching a maximum of about 2,500 ml. on day nine. Meanwhile, on the fourth hospital day digitalis had been started. On day eight he was found to be fibrillating, with an apical rate of 150 per minute. The digitalis was increased and he reverted to normal rhythm. Cardiac arrhythmia, however, recurred in the form of flutter. The sodium rose to 160 mEq./L., the chloride to 122 mEq./L. The blood pressure tended to become lower and reached a low of 74/65, but most of the time ranged around 90/60. On the eleventh hospital day he developed fever, the temperature rose to 38.7°C. and he died suddenly early on the morning of the twelfth hospital day. A single white blood cell count of 50,000 was recorded at the time of onset of the fever. A differential white count was requested at the same time. However, it was not done, and there was no subsequent white count. The sputum, which grew out only fungi shortly after admission, on the day before death grew out a heavy growth of Staphylococcus aureus. May we see the x-rays please, Dr. Elliott?

DR. GLADDEN V. ELLIOTT: This patient had a single examination of his chest on the day of admission to the hospital. There was a rather moderate cardiac enlargement, preponderantly of the left ventricle. Associated with this was a prominence of both major pulmonary arteries, the peripheral branches of which were engorged and indistinct in outline, suggesting pulmonary congestion. There was little fluid at either base. On the right, one segment of platelike or distoid atelectasis was apparent, and in

the left mid-lung field there was a small ill defined area suggesting a small patch of pneumonia. The discrepancy between the radiographic picture and the clinical picture of pneumonia was quite striking; actually, except for the small patch of distoid atelectasis, we ascribed all of these findings to pulmonary congestion.

DR. SCOTT: Now we have at least three problems to discuss: First, the nature of the precipitating illness; second, the etiology of the oliguria and, finally, the cause of death. First of all, let us discuss the nature of the infection, if indeed it were an infection. Certainly some of the symptoms described strongly suggested a respiratory disease. You will recall that he had a shaking chill followed by fever, cough and blood-tinged sputum, and a pain which was perhaps or even probably pleuritic. At the time of admission there were herpetic lesions on his upper lip and he had a leukocytosis of 17,000. Dr. Harford, can we do anything further to delineate the nature of this precipitating illness?

DR. CARL G. HARFORD: The facts as you have mentioned them point strongly to a diagnosis of acute bacterial pneumonia, or to pulmonary infarction with secondary bacterial infection. With respect to specific etiology, we are in an uncertain position because the blood culture was negative. The sputum culture disclosed fungi at first, then later a heavy growth of staphylococci which may not have been concerned with the terminal illness.

DR. SCOTT: Of course, he received a fair amount of treatment before he got to the hospital, not only with penicillin but with tetracycline as well; this may well have rendered his blood culture negative and eliminated any bacteria in the sputum, so that all we can do is speculate that he conceivably might have had bacterial pneumonia.

DR. HARFORD: In spite of the fact that very little can be seen on the x-ray it is perfectly possible to have a severe bacterial pneumonia with the clinical findings described.

DR. SCOTT: The clinical impression while he was in the hospital was that he probably did have pneumonia. It should be pointed out that his pulmonary signs at both lung bases and the dullness persisted essentially unchanged throughout the remainder of his hospital course. Dr. Massie, Dr. Harford has raised the question of pulmonary embolism; certainly pulmonary embolism could have caused a number of these symptoms, the fever, cough, blood-tinged sputum, pain and leukocytosis. Can it produce shaking chills?

DR. EDWARD MASSIE: I think that shaking chills may occasionally accompany a pulmonary infarction.

DR. SCOTT: And the electrocardiogram?

DR. MASSIE: The electrocardiograms consist of ten tracings. There is one dated February, 1951, which shows without doubt that he had had an anterior infarction. An interim tracing taken on April 29, 1953, is identical except for the presence of right bundle branch block. The right bundle branch block must have appeared between 1951 and 1953; it could have appeared shortly after the initial infarction in 1951 or at a later time. There were subsequently eight more tracings, all showing an anterior myocardial infarction and right bundle branch block. One can say from these tracings that the patient had an old anterior infarction. If he had a new one during this illness, it must have been one that did not exemplify itself in any manner. The earlier development of right bundle branch block, which can occur as a transitory phenomenon in pulmonary infarction, prevents us from using this abnormality to help us make a diagnosis of pulmonary infarction. All we can say definitely is that he had an anterior infarction in the past, without evidence of a new one during this terminal illness, and that he developed a number of arrhythmias, principally rapid auricular fibrillation and, terminally, auricular flutter with 2:1 block. This sequence could occur during uremia, during any terminal illness or in the presence of high fever, and would not be sufficient evidence to warrant a diagnosis of pulmonary infarction. In addition, there has been no change in the electrical axis of the heart. I would certainly not make a diagnosis of any fresh myocardial infarction of large size. I would think that something else might be present.

DR. SCOTT: Are there any other suggestions as to what this illness might have been?

DR. ALFRED GOLDMAN: I saw this man when he first came into the hospital. His illness began with a sore throat, and I made a diagnosis of a bacterial pneumonia in view of the history, the chills, fever, herpes, and the leukocytosis, and the rather rapid response to penicillin and streptomycin seemed to confirm my opinion.

DR. W. BARRY WOOD, JR.: Dr. Scott, with what happened after the acute infection one would have to consider the possibility that a beta hemolytic streptococcus was involved. It is

TABLE 1

FLUID BALANCE, BLOOD CHEMISTRY AND URINALYSIS DATA OBTAINED DURING HOSPITAL COURSE OF PATIENT H. F.

Hosp. Day	Weight (lb.)	Fluid Intake				Fluid (ml.) Output	Blood Chemistry					Urinalysis	
		Parenteral		Oral			NPN (mg. %)	Na (mEq./L.)	K (mEq./L.)	Cl (mEq./L.)	CO_2 (mEq./L.)	Sp. Gr.	Protein
		Type	Amount (ml.)	Amount (ml.)	Total								
1						0						Q.N.S.	Trace
2	154					0	100						
3	151½					300						1.019	Negative
4	153	.85% Saline	900	370	1,270	200	161	133.9	5.4	86	17.6		
5	150	.85% Saline	750	1,150	1,900	440	168	130.4	5.6	85	15.8		
6	149½	5% Glucose/water	300	0	300	595	208	131.1	6.2	93	15.0	1.007	Negative
7	146½	(Molar NaCl)	300	0	650	1,255 urine						1.006	Trace
		5% Glucose/saline	350			140 tube							
8*	144	(Molar NaCl)	200	0	200	2,250 urine	246	148.0	6.4	108	17.2	Q.N.S.	Trace
						675 tube							
9	141	5% Glucose/water	1,000	0	1,000	2,500 urine	212	147	4.1	116	19.9	1.010	Slight trace
						50 tube							
10	129	5% Glucose/water	2,000	0	2,000	900 urine	210	160.4	4.9	122	22.7		
						1,050 tube							
11†	129	10% Glucose/water	1,000	0	2,000	2,100 urine	210	160	5	112	30.5		
		5% Glucose/saline	1,000			550 tube							

* In Case 8, serum Ca was 8.6; inorganic P 10.1 mg. per cent.
† In Case 11, serum Ca was 9.0; inorganic P 8.5 mg. per cent.

interesting that the family noticed that the patient gained weight although he did not eat. Also, the decreased urinary volume began relatively early in an illness that started with a sore throat. No studies relating to the beta hemolytic streptococcus were done, other than the sputum culture. We do not know whether there were any streptococcal antibodies present. The patient was treated with penicillin, so that even if streptococci were there in the beginning they would not have been in the cultures of the sputum. We must consider the possibility that beta hemolytic streptococci produced acute glomerulonephritis in this man.

DR. SCOTT: Was the time interval satisfactory for making that diagnosis?

DR. WOOD: The time interval would depend upon when he developed the sore throat. Do we have more information on this point?

DR. GOLDMAN: I talked to the doctor who saw him at home; he said it was four days before hospital admission that he developed the sore throat.

DR. SCOTT: Apparently then the sore throat and the oliguria began very close together, the oliguria following the sore throat by not more than two days. Before we discuss his oliguria let us assume for a moment that this is lower nephron disease or hypoxic nephrosis. Infection has been incriminated as a cause for people developing this type of lesion. What specific types of infections are referred to in this general statement, Dr. Teschan?

DR. PAUL TESCHAN: The main infectious causes of acute renal insufficiency are those associated with bacteremia. The two types of bacteremia most commonly associated with this are bacteremia due to gram-negative bacilli, and that due to the staphylococcus. Other organisms certainly can account for the classical picture that follows. These patients do not die of the initial infection.

DR. SCOTT: The infections, then, that produce acute renal failure are usually severe fulminating infections, associated either with bacteremia or with clinical shock. As I have tried to indicate in giving the history there is no indication that this man was ever in clinical shock. How then can we evaluate this infection?

DR. TESCHAN: It is tempting to start with the fact that the patient had a shaking chill, which can sometimes be associated with bacteremia, and then on admission was found to have a blood pressure of 90/60. It is important to remember that blood pressures are often maintained by virtue of a renal vasoconstriction, or may be. The blood pressure reading of 90/60 gives us no definite idea as to what may be happening to the renal vasculature. We ought to recall that in the first forty-eight hours the lysis of the fever was very precipitous. Falls in blood pressure are very common under these circumstances. So whether due to an actual bacteremia, or due to a rapid fall in blood pressure after this patient was hospitalized, a vascular shut-down of the kidney might have occurred.

DR. SCOTT: Let us go ahead then and discuss the oliguria. His weight gain while at home must have been, in retrospect, significant, although little attention was paid to this at the time the patient came into the hospital. What kind of situations, Dr. Wood, would produce a weight gain of 6 to 10 pounds under these circumstances?

DR. WOOD: There are many things that will cause weight gain. For example, practically any acute infection will bring about a retention of salt and water with a resultant gain in weight. The same thing can be said about hepatitis, a disease that was carefully studied in this regard by Dr. Hoagland at the Rockefeller Institute Hospital; he demonstrated clearly that there is a water and salt retention during the acute phase of infectious hepatitis with resultant weight gain. But weight gains of 6 to 8 pounds seem excessive for these conditions, and with the history of oliguria we can best attribute it in this case to some renal component. Patients with acute nephritis who experience sudden oliguria, of course, gain weight very rapidly. Anything that will bring about a decrease in output of water by the kidney may lead to retention of this kind and gain in body weight. I would guess here that this was a manifestation of the renal failure. In addition, if the patient developed cardiac failure, of course, that would certainly accelerate the water retention. In this case this is pertinent, because we have a story suggestive of left ventricular failure. On the other hand, as I read the rest of the protocol I become more and more impressed by the renal part of this story and less impressed by the cardiac, but I may be misled.

DR. SCOTT: Let us then discuss the urinary findings. During the period of hospitalization the patient had ten urinalyses. The specific gravity varied as indicated in the table from 1.019 to 1.006. The urine was always acid, the pH ranging from 4.5 to 6.5. Protein was never present in

greater amounts than a trace, and on several occasions no protein was present at all. In respect to sediment, at the outset there were numerous coarse granular casts, 15 to 30 white cells, and no red cells per high power field. During the ensuing days, on five of the ten urinalyses, red cells were described as being present in the urine, but on four of these occasions, never more than 3 red cells per high power field. On the day before death his urine contained 15 to 20 red blood cells per high power field. Leukocytes remained present in large numbers throughout his course, ranging from a low of 8 to 10 per high power field to 30 to 40 per high power field. The numerous granular casts gradually became fewer in number and were replaced by an occasional hyaline cast near the end of his life. We have then a urine which varied in specific gravity within fairly wide limits, the highest specific gravity being on the third hospital day. The urine remained acid and contained minimal amounts of protein, few red blood cells except on one occasion, large numbers of white cells, and initially large number of granular casts which later disappeared and were replaced by hyaline casts. We have to discuss whether this was acute glomerulonephritis, a tubular lesion of some kind, or not acute renal failure at all. Dr. Daughaday, how do you interpret these urinary findings?

Dr. William H. Daughaday: The real question is, can you have acute glomerulonephritis with so few red cells and so little damage to the glomerular membrane as evidenced by protein leaking through. I do not see how this possibility can be completely eliminated, but these urinary findings fit the picture of lower nephron ischemia or hypoxic nephrosis better than they do a glomerular lesion.

Dr. Scott: It might be worth while to read from an article by Swann and Merrill[1] with respect to the urinary findings in acute renal failure. They state, "Proteinuria is usually intense at the onset of oliguria and progressively diminishes during the remainder of the course. After the first few days it is usually not more than 1 to 2 + on qualitative tests. It has been stated that the urine is markedly acid at the onset of acute renal failure. After the first day or two, however, the urinary pH remains between 5.5 and 7.0 during the remainder of the oliguric stage in nearly all cases in the author's experience. The specific gravity approaches 1.010 during the oliguric phase. While a relatively low specific gravity usually develops shortly after the onset, in some cases the specific gravity falls progressively from 1.020 to 1.010 during the first week of oliguria. A urinary specific gravity of 1.015 to 1.020 (corrected for proteinuria) during the first few days of oliguria does not rule out acute renal failure. . . . Erythrocytes are more numerous in the urinary sediment early in the oliguric stage, and usually progressively diminish thereafter. On the other hand, leukocytes often become more numerous later in the oliguric period. As discussed under the diuretic phase there is evidence that at least some of these are of renal origin. Granular casts in small numbers are usually present during oliguria." According to Swann and Merrill the urinary findings in this case support Dr. Daughaday's opinion that this is acute renal failure.

Dr. Robert J. Glaser: What is known about this man's renal state at the time of his first illness? It would be helpful to know that, because if this were glomerulonephritis related to a sore throat which occurred four days before he came to the hospital one would have to postulate that it was a recurrence. In general, the latent period would be expected to be somewhat longer if this were his first episode. On the other hand, if recurrence of acute glomerulonephritis follows a previous attack which had left residual damage, this sequence may develop. I agree with Dr. Daughaday that the urinary findings are unusual for glomerulonephritis, as is the absence of hypertension, but one could make a case for this having been a recurrence of glomerulonephritis.

Dr. Goldman: In his hospital record three years ago his urinalyses were negative; his physician informed me that eighteen urinalyses in the past two years were also always negative.

Dr. Wood: That information is terribly important. It is hard, Dr. Scott, to maintain a diagnosis of recurrent glomerulonephritis in view of those reports of consistently negative urines. What bothers me is that this man on his fourth day of illness had a non-protein nitrogen of 100, which is an unusually rapid rise in lower nephron disease. It is not very common for that to occur until the patient gets very sick and anemic. So there is a little question as to whether this is lower nephron disease alone. On the other hand, if we believe the statement that there was narrowing of the retinal vessels, that suggests that

[1] Swann, R. C. and Merrill, J. P. The clinical course of acute renal failure. *Medicine*, 32: 251, 1953.

possibly this patient had had some vascular disease in the past, and may even have been hypertensive before his coronary occlusion occurred. In that case he would then possibly have had kidneys that were damaged by previous vascular disease upon which was superimposed this acute episode, whatever it was.

DR. DAUGHADAY: Is there any possibility this man could have been exposed to a toxin? What were his habits?

DR. SCOTT: He was not an alcoholic. Dr. Goldman had the patient's wife bring in samples of all the pills that were in the medicine cabinet and found nothing of significance. He had not been exposed to any fumes.

DR. MELVIN GOLDMAN: In this case one must also think of cortical necrosis of the kidneys. The sudden onset of oliguria and anuria and the fact that his blood pressure remained low throughout his hospital course suggest this diagnosis. It is unusual for the blood pressure in hypoxic nephrosis to remain down; it usually rises as the non-protein nitrogen goes up. The leukocytosis suggests cortical necrosis of the kidneys to me and I would like to offer as a diagnosis that he suffered from a severe infection, myocardial infarction and shock with renal cortical necrosis.

DR. SCOTT: Shock was never really present in this man, Dr. Goldman. Don't you get hematuria in cortical necrosis?

DR. TESCHAN: Our impression is that hematuria is almost uniform in cortical necrosis, at least as it is described in postpartum women. I was going to make one other comment. There are two other fragments of evidence that suggest that there was some antecedent renal disease. The presence of a carbon dioxide combining power of 17.6 mEq./L. on the fourth hospital day is a little low for either an acute renal shutdown due to glomerulonephritis, or for acute renal failure on the basis of tubular destruction. Perhaps not quite so convincing is the serum phosphorus of 10.1 mg. per cent on the eighth hospital day. That is a little high for that sequence of events in most patients with hypoxic nephrosis.

DR. SCOTT: Would you comment on the electrolytes, Dr. Schroeder?

DR. HARRY SCHROEDER: Of course, the electrolyte concentration depends on how much salt the patient contains when he is oliguric. You can get any kind of electrolyte picture in this type of disease. Usually there is a hyponatremia, because the patient is drinking water and not putting it out. If one took in normal saline during a renal shutdown, one could expect normal saline to go into the extracellular fluid. One cannot say that any particular feature is essential for hypoxic nephrosis or for the presence of oliguria.

DR. SCOTT: What about the molar saline solution that was given. How do you interpret what happened after that?

DR. SCHROEDER: Apparently he had been trying to diurese before he got the molar saline; perhaps that fluid helped his serum chlorides a little bit; it certainly seemed to elevate his sodium concentration. I think that molar saline in general in the presence of a low carbon dioxide content should not be given unless it is covered by concurrent sodium lactate. One prefers to get a little more lactate than molar saline if one is going to treat these patients in this way because normal saline is in essence nearly $\frac{2}{7}$ of hydrochloric acid and $\frac{5}{7}$ of sodium chloride.

DR. SCOTT: Was his terminal hypernatremia due to the fact that he got too much molar saline?

DR. SCHROEDER: Something happened in which he put out a great deal of urine and probably did not put out much salt.

DR. SCOTT: There must be some redistribution of sodium, because when he began to have his diuresis his serum sodium concentration stayed at normal levels for five or six days before it rose to 160 mEq./L.

DR. SCHROEDER: It is possible that either there was a redistribution of sodium or there was excessive output of plain water with very little sodium in it. You will notice that his weight dropped 12 pounds in one day, which is a rather surprising finding in view of a urine output of 2,500 ml. at that time.

DR. SCOTT: There was a question mark after that in the record but it was confirmed the next day. I am sorry that our time is up, because there are many more aspects of this patient's disease which we could discuss if time permitted. In respect to his terminal course you will recall that he developed this alleged leukocytosis of 50,000, which was not confirmed and conceivably could be a technical error, although we shall have to accept it at its face value. He then developed cardiac arrhythmias and fever on his last day and then died suddenly. Does anyone care to make any comments as to what is going on at this stage of his illness?

DR. MASSIE: That was a terminal arrhythmia which may occur in any severe disease.

DR. SCOTT: In the patients described by Swann and Merrill there were thirty-nine deaths in eighty-five patients. Twenty-five per cent of their thirty-nine deaths occurred during the diuretic phase, not the oliguric phase, and five of these deaths occurred suddenly in patients who were improving. At autopsy nothing was found to explain the cause of death, so presumably it was due to the heart. If I interpret the feelings of this group correctly, this patient probably started off with a severe infection of some kind, perhaps bacterial pneumonia, and then developed, for reasons which are not entirely clear to us, hypoxic nephrosis. There is an outside possibility that this was recurrent glomerulonephritis. Are there modifications of these comments?

DR. WOOD: This expresses your own opinion also, does it not Dr. Scott?

DR. SCOTT: Yes, it does.

PATHOLOGIC DISCUSSION

DR. JOHN D. KEYE: The skin at autopsy showed a fine flat erythematous rash over the trunk and extremities. In the right thoracic cavity there were 70 ml. of thin amber cloudy fluid which did not clot, and less than 10 ml. of a similar fluid were present in the left cavity. The pericardial sac contained a small amount of an amber fluid and a fine fibrinous exudate that formed adhesions between the epicardium and the pericardium. The heart weighed 475 gm. A large scar involved the anterior half of the interventricular septum and the anterior wall of the left ventricle with reduction of those portions of the wall of the ventricle to a thickness of only 3 mm. A recanalized thrombus occupied the anterior descending branch of the left coronary artery. There was very little arteriosclerosis. The myocardium not involved in the healed infarct was remarkable only for a slight greyish mottling of its color. The lungs were light and slightly emphysematous. The only important lesions were a slight congestion and edema in the lower lobes and a thick mucopurulent exudate in the bronchi. The kidneys were very slightly enlarged; the right weighed 200 gm. and the left 155 gm. The capsules were easily stripped revealing a finely granular surface that was intensely congested and bulged when cut. There were ecchymoses and petechiae in the major and minor calyces.

DR. DAVID E. SMITH: The gross findings of this autopsy were hardly more revealing than had been the clinical course of the patient. To begin with the principal feature of this case, the first illustration (Fig. 1) is of a slide of the kidney. It shows a remarkably intense infiltration of cells in the interstitial tissue with resultant wide separation of the tubules and glomeruli. The tubules themselves are relatively well preserved and show only a slight degree of such a non-specific change as cloudy swelling. The glomeruli contain no lesions. These infiltrating cells are plasma cells, lymphocytes and an occasional mononuclear cell as is shown in Figure 2. This is a fairly typical picture of diffuse non-suppurative interstitial nephritis. There is no evidence of any tubular lesion that would lead us to suspect hypoxic nephrosis.

Other organs also contain evidence of an interstitial inflammation. Scattered throughout the myocardium there are a number of foci of rather intense cellular infiltration in the interstitial tissue. (Fig. 3.) The infiltrating cells here are also lymphocytes and plasma cells, and there is relatively little in the way of reaction in the myocardial fibers. The infiltrates are not associated intimately with the blood vessels and the vessels themselves show no changes. Aside from the rather concentrated areas of inflammation, some degree of infiltration of the interstitial tissue is present in almost every microscopic field of the myocardium. The epicardium in sections is covered by a layer of fibrin but also shows mononuclear cells deep in the epicardial fat to a degree greater than one expects in the usual fibrinous pericarditis of uremia alone. The adrenal cortex (Fig. 4) also shows the same mononuclear interstitial inflammation and a similar, although less intense, infiltration is present in the pancreas and in the portal spaces of the liver.

The usual causes of interstitial non-suppurative nephritis are remote infections and septic states that are thought to operate through an allergic or hyperergic mechanism.[2] It is a lesion, for instance, that is one of the renal complications of scarlet fever, and on other occasions appears to be a result of drug sensitivity, particularly to the sulfonamides. It has not to my knowledge been reported as a result of therapy with the more recently developed antibiotics. In this case

[2] ALLEN, A. C. The Kidney, Medical and Surgical Diseases, pp. 299–302. New York, 1951. Grune and Stratton.

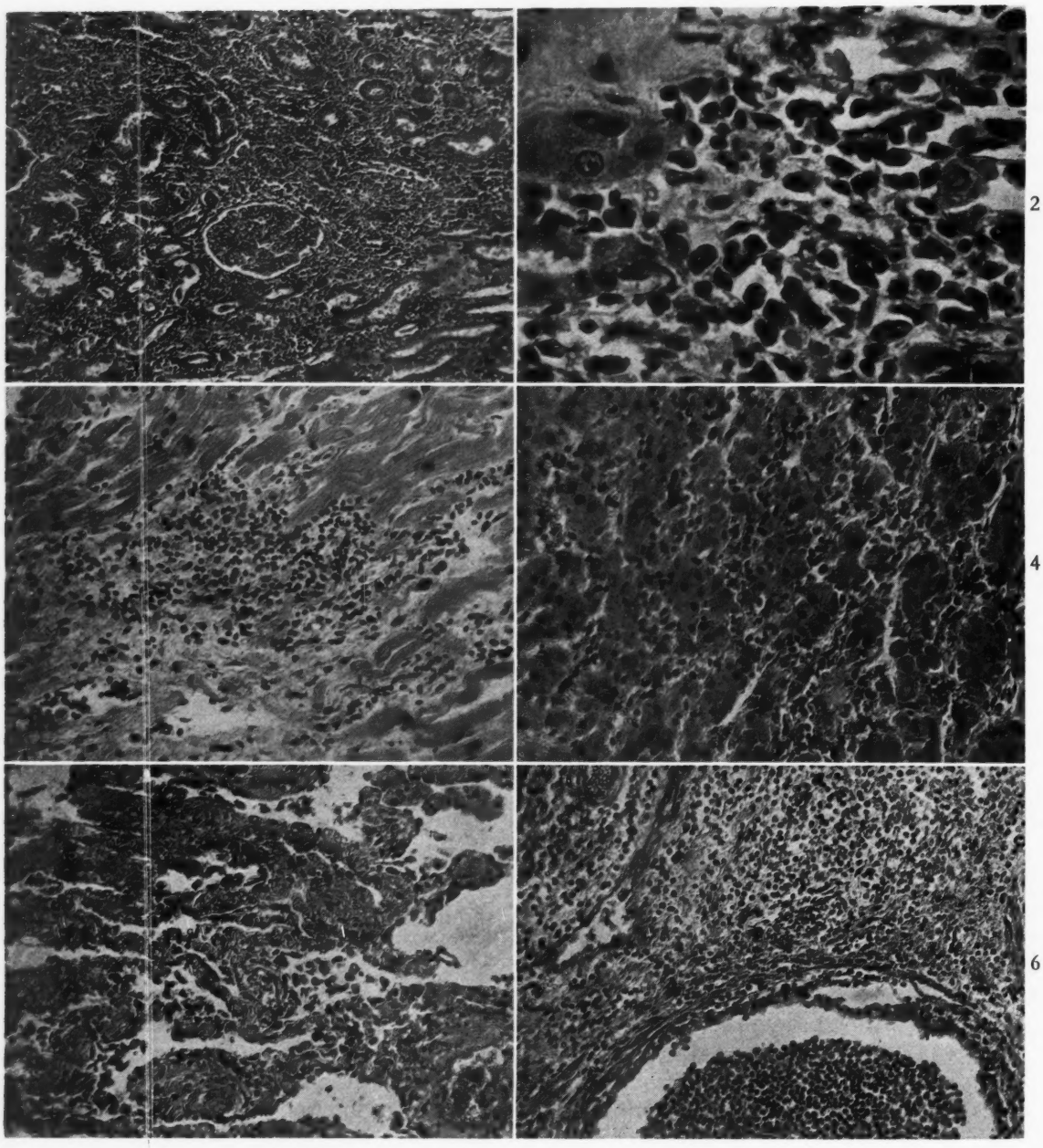

FIG. 1. Intense diffuse interstitial infiltration of cells in the kidney without intrinsic lesions in the glomeruli or tubular epithelium in acute interstitial nephritis.

FIG. 2. The interstitial infiltrate in the kidney at higher magnification showing it is predominately composed of plasma cells.

FIG. 3. One of the foci of more intense interstitial inflammation in the myocardium.

FIG. 4. Diffuse interstitial infiltration of mononuclear cells in the adrenal.

FIG. 5. One of several foci in the lungs: thickened alveolar walls and organized exudate in the alveoli interpreted as the residue of pneumonia that was probably responsible for the early symptoms.

FIG. 6. Acute purulent exudate in the acini and interstitial inflammation in the prostate.

the exhaustive clinical inquiry apparently eliminated sulfonamides as a cause and the lack of eosinophils in the accompanying myocarditis also points away from drug sensitivity. On the other hand, the type of reaction in the heart following local infections elsewhere, as in scarlet fever, can resemble that seen in this case although plasma cells are not so often seen. We looked in various sites for a local infection. The patient did have an acute bronchitis at the time he died, but it would be difficult to incriminate that as the primary infection. None of the postmortem cultures revealed a likely bacterial agent. There are several areas in the lungs, such as that shown in Figure 5, in which there is considerable fibrous thickening of alveolar walls with little organized exudates suggestive of unresolved and organized pneumonia. This would be consistent in time with the episode of pleuritic pain four days prior to admission, and indicates that a pneumonia was present, and might have initiated the subsequent renal lesions although pneumonia is not reported as a common antecedent of these lesions. The urinary bladder showed denuded mucosa and a slight inflammatory infiltration with congestion of the mucosa that is typical of cystitis, and could account for the erythrocytes this man had in his urine, but would not be a likely antecedent of interstitial nephritis. Figure 6 shows an active acute prostatitis with acini that are filled with polymorphonuclear leukocytes spreading into the interstitial tissue. Prostatitis, however, is also not usually recognized as a source from which these renal and cardiac lesions may arise. Sections of the erythematous rash of the skin noted at the time of autopsy show some thickening and acanthosis of the epidermis and inflammation about the hair follicles, but seem to be of a non-specific nature that is not compatible with scarlatina. If such a diagnosis could have been established, it would have made this a fairly typical case.

After reviewing all this evidence, and since none of the acute inflammations present at the time of death can be considered likely causes of the nephritis and myocarditis, we can only agree with the suggestion of Dr. Wood that there may have been an undetected episode of streptococcic pharyngitis at the onset of the patient's symptoms.

The classic description of acute interstitial nephritis was written by Councilman in 1898.[3] It is consoling to note that even the most recent discussions[4] stress the difficulties of recognizing this condition before death. The early appearance in the course of an infection of moderate or severe oliguria, or even anuria, with rapidly rising azotemia is most suggestive. The lack of hypertension or edema and slight or insignificant proteinuria are characteristic, and are well illustrated in the present case. Occasionally, hematuria or a slight pyuria have been described, but in this case it seems more likely that the cystitis and prostatitis were the source of such findings. The short time interval between the postulated infection and the onset of oliguria two days later as well as the subsequent rapid rise of the non-protein nitrogen in this case are compatible with the experiences of others with this disease.

In summary, this case presents the definite anatomic lesion of interstitial non-suppurative inflammation in the kidneys and the heart with evidence of a lesser degree of interstitial inflammation in the pancreas, adrenals and liver. The cause of this is not proven, but it is strongly suspected that it followed an infection, most probably caused by the hemolytic streptococcus.

Final Anatomic Diagnosis: Acute interstitial nephritis; interstitial inflammation in the heart and adrenals; fibrinous pericarditis; acute bronchitis, hemorrhagic cystitis and prostatitis.

[3] Councilman, W. T. Acute interstitial nephritis. *J. Exper. Med.*, 3: 393–420, 1898.

[4] Fishberg, A. M. Hypertension and Nephritis, 5th ed., pp. 661–665. Philadelphia, 1954. Lea and Febiger.

Case Reports

Hypothermia Following Cortisone Administration*

GERALD H. KASS, M.D.†
New York, New York

MARKED hypothermia, other than that physically induced, is not common. The purpose of this report is to present a case of hypothermia following the administration of cortisone.

A thirty-two year old, white male entered the Bronx Veterans Administration Hospital complaining of intermittent high fever, joint pains and a generalized skin rash. His illness began one year prior to admission during which time he had one episode of severe substernal pain that had been diagnosed as pericarditis. In the year prior to admission he received penicillin, aureomycin, aspirin and a two-week course of cortisone, 200 mg. daily. The cortisone caused remission of symptoms only during the time of administration, with no untoward effects. Just prior to admission a generalized, erythematous rash erupted.

The patient, a well developed, well nourished white male, was acutely ill with a temperature of 104°F. His skin was hot and moist. Blood pressure was 98/80 and a sinus tachycardia was present. His rash was generalized and asymmetrical, most marked over his neck and chest but also involving all parts of the body including the palms of his hands and the soles of his feet. Purplish periorbital edema was present. Submaxillary and posterior cervical lymphadenopathy was noted. The remainder of the physical examination was within normal limits. The patient was considered to have one of the collagen diseases.

The initial hemogram was within normal limits; however, leukopenia was found on three different occasions during hospitalization. Urinalysis revealed 3-plus albumin and granular casts. The Wassermann test, febrile agglutinins, hemagglutination test for rheumatoid arthritis,[1] Trichinella complement fixation test, antistreptolysin titer and blood cultures were negative. There were no abnormal chemical findings except for a 4-plus cephalin flocculation test. The patient had creatinuria. All x-rays of the chest were within normal limits.

The patient was treated symptomatically pending the establishment of a definitive diagnosis. On the ninth day of hospitalization a skin and muscle biopsy‡ was reported as strongly suggestive of dermatomyositis. The patient appeared desperately ill and cortisone was administered in large doses. He received 100 mg. initially and three additional 100 mg. doses equally spaced over the next sixteen hours. His temperature soon fell to normal but continued downward at a precipitous rate. (Fig. 1.) Aspirin was stopped and his temperature seemed to stabilize at 96°F. over the next eight hours but once again it dipped sharply to a low of 87.8°F. By this time all medication including cortisone had been stopped. During this period the pulse varied directly with the temperature. (Fig. 1.) An electrocardiogram revealed a sinus bradycardia with a corrected Q-T interval of 0.60 seconds whereas it had shown a sinus tachycardia previously.

The patient remained conscious although lethargic. He continued to sweat, did not complain of feeling cold and did not shiver. Aside

‡ This biopsy result as well as those of two subsequent biopsies was reported by Dr. Arthur C. Allen, Consultant in Pathology.

* From the Medical Service of the Bronx Veterans Administration Hospital, New York, N. Y. Reviewed in the Veterans Administration and submitted with the approval of the Chief of Professional Services. The statements and conclusions presented by the author do not necessarily reflect the opinion or policy of the Veterans Administration.

† Present address: Electrocardiographic Laboratory, The Mount Sinai Hospital, New York, N. Y.

from a short interval when it was unobtainable, his blood pressure remained at slightly lower levels than recorded on admission.

The neurologic changes were the most impressive. His deep tendon reflexes responded normally and equally but his superficial reflexes were absent. His upper extremities showed cogwheel rigidity and athetoid movements. There was ataxia of the upper and lower extremities. Loss of position and vibratory sense of great toes was demonstrated. The spinal fluid was crystal-clear and under normal pressure. The only abnormal spinal fluid findings were elevation of the protein to 127 mg. per cent and glucose to 100 mg. per cent. A blood sugar was not obtained at this time.

Additional blankets were used to conserve heat loss, atropine was given to control sweating and antibiotics were administered to prevent infection. On the second day his temperature rose to 94°F. At this time there was some depression of mental activity but he remained grossly oriented. The athetoid movements of his upper extremities disappeared but tremors replaced them. His reflexes became hyperactive. On the third day his temperature rose to 96°F. and later to 98°F. No other abnormalities were noted on physical examination and there were no other apparent ill effects due to the hypothermia.

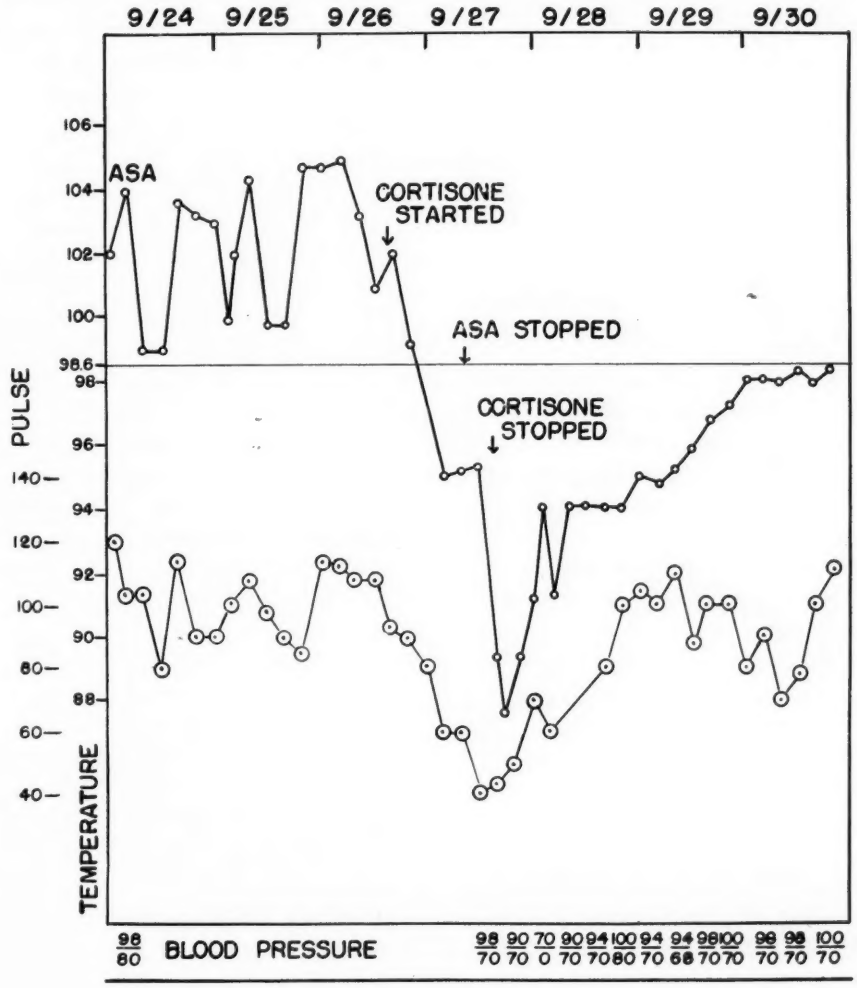

FIG. 1.

However, several days later the patient once again became acutely ill with high spiking temperature, arthralgias, muscular pain and tenderness. Para-aminobenzoic acid was given to the patient. The temperature fell to normal but he soon became febrile once again. The dose of PABA was increased gradually to 20 gm. each day in divided doses. His temperature became normal and at this time the patient looked and felt his best since admission.

During this episode a second spinal fluid examination revealed a first zone colloidal gold reaction and protein of 80 mg. per cent. An

electroencephalogram revealed diffuse, low grade, cerebral dysrhythmia. A second skin and muscle biopsy was reported as compatible with diffuse vascular disease or embolic phenomena. A butterfly rash appeared over his nose and malar eminences and a biopsy of this was consistent with disseminated lupus erythematosus or dermatomyositis. A cantharides blister preparation yielded cells showing the L. E. phenomenon.

Approximately ten weeks after admission the patient was discharged, markedly improved, still taking PABA. Within a week he was readmitted with fever, muscle tenderness and arthralgias. The laboratory findings were within normal limits. PABA was stopped and, in view of the patient's condition, readministration of cortisone was considered despite the patient's previous hypothermic reaction. With proper precautions, cortisone in 25 mg. doses was given four times a day, the patient being closely observed before and after each dose. His symptomatic response was dramatic. The temperature fell to 96°F. during the first day of administration. On the following day his temperature ranged between 97° and 98°F. Cortisone was stopped and his temperature rose to normal. He was soon discharged, improved, and has been seen in the follow-up clinic periodically for approximately one and one-half years. He is quite well and has been able to perform light labor. At present he shows no signs of activity of disseminated lupus erythematosus.

COMMENTS

Body temperature is regulated through the hypothalamic centers. Hypothermia can result from decreased heat production, increased heat loss or both. The converse is true for hyperthermia.

In animal experiments, lesions placed in the hypothalamus and the supraoptic nuclei produce disturbances in temperature regulation. Lesions placed in the region of the anterior commissure can cause transient hyperthermia. A profound and prolonged hyperthermia can be produced by bilateral lesions placed in the anterolateral nuclei of the hypothalamus. These lesions, while leaving the animal defenseless in its protection against heat, do not interfere with its ability to protect itself against cold. If the bilateral lesions are placed in the posterior hypothalamus, especially in the lateral portions, hypothermia results.[2]

There are postmortem observations in humans which correlate with these animal experiments. In four cases in which hypothermia had been a prominent symptom Davison found that the lesions involved the lateral and caudal portions of the hypothalamus. In a case in which hyperthermia had been the prominent symptom Davison found lesions in the anterior and middle hypothalamus.[3] In three cases of hyperthermia Zimmerman found lesions in the ventromedial hypothalamic nuclei, destruction of a mammillary body or interruption of the mammillothalamic tract. In a fourth case in which hypothermia had been present Zimmerman found lesions in the posterolateral hypothalamic nuclei, among other areas of destruction.[4]

Hypothermia may be the resultant of causes other than lesions found in the hypothalamus. It may occur in exposure, in hypoadrenalism, hypothyroidism, hypopituitarism, in shock and the shock-like states found in cholera and typhoid fever.

Normal temperature is difficult to depress with drugs except those which cause profound narcosis, generalized vasomotor paralysis or collapse. In rabbits, preparations of ACTH have been found to depress temperature 1 to 3°C. below normal. In pyrexia established by means of pyrogens, ACTH is effective in reducing the animals' temperature to normal or even subnormal limits.[5] Likewise, cortisone is efficacious in reducing the animals' sensitivity to pyrogens. In investigating ACTH and cortisone effect on body temperature it is necessary to determine their efficacy against cold. No significant increase in survival occurs in exposed rats treated with ACTH or cortisone as compared with the control group.[6]

Although ACTH has an antipyretic effect in man, a hypothermic effect has not been recorded.[7] In the case of exposure reported by Laufman, in which the temperature was recorded at 64.4°F., hyperglycemia was found initially. Since the patient had undergone severe stress, Laufman gave 200 mg. of cortisone intramuscularly. It would be difficult to evaluate the action of cortisone but it did not cause any further hypothermia for the patient's temperature continued to rise after its administration. Incidentally, this patient also had a sinus bradycardia and prolonged Q-T interval.[8]

Cortisone has been reported to have central nervous system effects and may precipitate seizures,[9,10] which occur in disseminated lupus erythematosus, however, without cortisone therapy.[11–13] This patient had definite neuro-

logic signs involving basal ganglia as well as the hypothalamus. Neurologic involvement is supported by the high spinal protein and the abnormal electroencephalogram noted. However, these neurologic signs could be the results of the hypothermia rather than a specific effect of the cortisone. The high spinal fluid sugar may be related to a transient hyperglycemia secondary to cortisone. A blood sugar was not determined to verify this hypothesis.

In this case there was increased heat loss as evidenced by the patient's continued perspiration despite a temperature below 90°F. At first a condition similar to shock was present. There was peripheral vasodilation, sweating and unobtainable blood pressure; however, sinus bradycardia rather than sinus tachycardia was present. Since the mechanisms controlling temperature were deranged temporarily, a hypothalamic lesion must be considered. The patient's high fever over a period of weeks may have decreased the activity of the hypothalamic centers. Because peripheral arterial occlusions do occur during cortisone therapy, thrombosis of one of the small arteries supplying the hypothalamus might be postulated except that the hypothermic state was transient. Since the patient continued to sweat, did not feel cold and did not shiver despite his temperature of 87.8°F., a posterior hypothalamus lesion must be considered. These signs and symptoms are quite similar to those associated with experimental lesions of the posterior hypothalamus as a result of which the animal is not able to protect itself against cold.

The best explanation of the facts would seem that large doses of cortisone acted on the posterior hypothalamus and the basal ganglia, which may or may not have been damaged by hyperpyrexia or, less likely, by the disease process itself. When cortisone was withdrawn, recovery took place slowly over a three-day period. When cortisone was administered again in smaller doses, hypothermia recurred but to a lesser degree.

It is unlikely that this is a case of drug allergy or idiosyncrasy. The patient had no ill effects from a two-week course of cortisone prior to his hospitalization. He did not show any of the common toxic signs due to cortisone or any symptoms referable to allergic phenomena.

SUMMARY

In a case of presumed disseminated lupus erythematosus marked hypothermia, reaching a low of 87.8°F., followed the administration of cortisone. Subsequent readministration of a much smaller dose again produced mild hypothermia. The most likely mechanism is an action on the temperature regulating centers of the hypothalamus.

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Unilateral Clubbing of the Fingers Due to Absence of the Aortic Arch*

E. R. Dorney, M.D., N. O. Fowler, M.D. *and* E. P. Mannix, M.D.
New York, New York

Complete absence of the aortic arch is an extremely rare occurrence and, according to most authors, incompatible with more than a few months of life. Taussig[1] described this clinical entity in her book on congenital heart disease and stated that she has never seen an example without other associated anomalies. Maude Abbott[2] listed seven examples of aortic atresia, one of which seems to correspond to the patient to be described. Evans[3] recorded three cases, two of which were in conjunction with ventricular septal defects, and one with a patent foramen ovale. The longest survival in this series was twenty-two days. Gaspar[4] presented a single case of a patient with a high ventricular septal defect and a patent foramen ovale who lived six months. He did not believe that the cardiac abnormality *per se* was responsible for death in his case and also stated that eight similar cases had been reported but failed to give documentation.

CASE REPORT

This five year old Negro girl was admitted for exploratory thoracotomy for cyanotic congenital heart disease. She was born at the Morrisania Hospital September 9, 1948, and weighed 5 pounds, 5 ounces at birth. Her mother had been well during pregnancy and had not been receiving any medication. Delivery was uneventful.

The patient was re-admitted to the Morrisania Hospital on November 22, 1948, with a complaint of vomiting, non-projectile, of one day's duration, and a "cold" with a running nose for three days. She had eaten poorly and failed to gain weight since birth. No previous dyspnea or cyanosis had been noted. After admission, the child was treated with penicillin and mercuhydrin and was then digitalized. X-ray showed congestive changes in both lung fields and a dense shadow occupying the entire left lung field suggestive of pulmonary atelectasis. The child did well and on December 29th was transferred for further observation to Beth Israel Hospital where fluoroscopy and films of the chest on January 3, 1949, showed marked enlargement of the heart to the left with very prominent pulmonary artery segment. The secondary branches were prominent and dilated. The barium-filled esophagus had a normal course.

The patient gained 5 ounces in the hospital and was discharged in good condition. The impression at the time was that she had an interauricular septal defect.

On February 15, 1953, she was admitted to the Brooklyn Hospital and an attempt at cardiac catheterization was made but was discontinued because of excessive ventricular irritability. She was re-admitted on July 27th and catheterization was carried out on July 28th.

On admission, physical examination revealed a small four and a half year old child who weighed 36 pounds. Systolic and early diastolic blowing murmurs were heard over the pulmonary area, with a systolic thrill palpable in the same area. The pulmonic second sound was very loud. The lungs were clear. The liver and spleen were not palpable. There was no cyanosis of the lips. Clubbing and cyanosis of the left hand and both feet was noted but these findings were not present in the right hand. (Fig. 1.) Electrocardiogram revealed right ventricular hypertrophy. Roentgen examination of the chest showed increased vascularity of the lung fields with no intrinsic pulsations of these vessels. There was a marked enlargement of the pulmonary artery (Fig. 2) and the right ventricle. Auscultatory blood pressure in the lower extremities was not obtainable but the systolic

* From the Cardiac Laboratory, Brooklyn Hospital, Brooklyn, N. Y., and the Departments of Medicine and Surgery, State University of New York, New York, N. Y. Supported by the Joseph May Fund, Brooklyn Hospital.

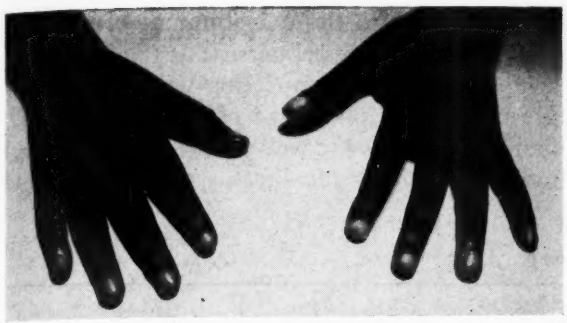


FIG. 1. Photograph of left and right hands showing clubbing of fingers of the left hand.

pressures obtained in the right arm and leg by the palpatory method were equal.

At catheterization on July 28th the cardiac catheter was passed from the pulmonary artery into the aorta through a patent ductus arteriosus. (Fig. 3.) The pressures showed marked pulmonary hypertension; the pulmonary artery systolic and diastolic pressures were each a few millimeters higher than the aortic pressures. (Table I.) The right atrial pressure was normal. The right brachial arterial oxygen content was much higher than that in the femoral artery. This indicated entrance of venous blood into the aorta past the point of the innominate artery. Unfortunately, a right ventricular sample could not be secured because of ventricular irritability, so that the possibility of an additional interventricular septal defect could not be excluded.

It was thought from the catheterization data, the x-ray and physical findings that the patient had a patent ductus arteriosus with pulmonary hypertension and reversal of flow. The possibility of a patent interventricular septum was also considered. Angiocardiograms were attempted on two occasions but were technically unsatisfactory.

The patient was discharged but was readmitted on November 9, 1953, for exploratory thoracotomy. Consideration was given at this time to the risk of operation in a patient with supposed pulmonary hypertension and patent ductus but it was felt that, if successful, a beneficial result might be obtained; whereas if the defect were left untouched a shortened life of invalidism was the only alternative.

Operation was performed on December 18, 1953. On opening the chest an enlarged right ventricle could be seen from which a single, large, widely dilated arterial trunk originated. This trunk, the pulmonary artery, gave off the left subclavian artery and was continuous with

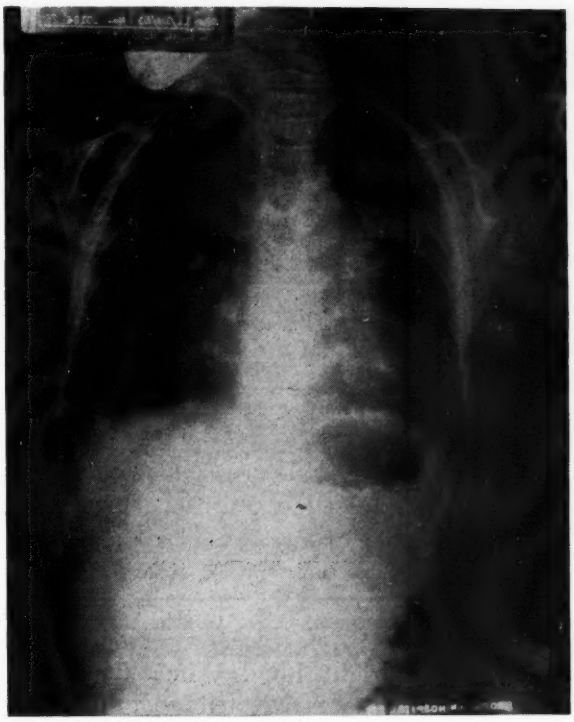


FIG. 2. Roentgenogram of chest showing dilated pulmonary artery segment and increased vascularity of the lung fields.

FIG. 3. Roentgenogram taken during catheterization. The catheter is shown passing from the right ventricle into the pulmonary artery and then into the descending aorta.

the descending aorta. It also gave off two other large vessels, one of which (the left pulmonary artery) entered the hilum of the left lung; and the other (the right pulmonary artery) coursed dorsally with reference to the main pulmonary artery and disappeared in the direction of the hilum of the right lung. When the dilated pulmonary artery was reflected forward, another much smaller vessel could be seen arising from the normal aortic site. This vessel went directly cephalad through the thoracic outlet into the neck and gave off no branches within the thoracic cage; it was in no way connected with the pulmonary artery or with the descending aorta. (Fig. 4.) After careful dissection and identification of all vessels, the chest was closed. The postoperative course was uneventful and the patient was discharged on January 6, 1954.

TABLE I
CATHETERIZATION DATA

Pressures (in mm. Hg)		Oxygen Concentration (in cc./100 cc.)	
Right atrium	4.5	Right atrium	9.5
Right ventricle	84/?*	Right ventricle	No sample
Pulmonary artery	107/81	Pulmonary artery	13.6 and 15.0
Aorta	105/75	Right brachial artery	19.5 (92% sat.)
		Femoral artery	15 and 15.2 (72% sat.)
		Aorta	14.8

*During short paroxysm of ventricular tachycardia.

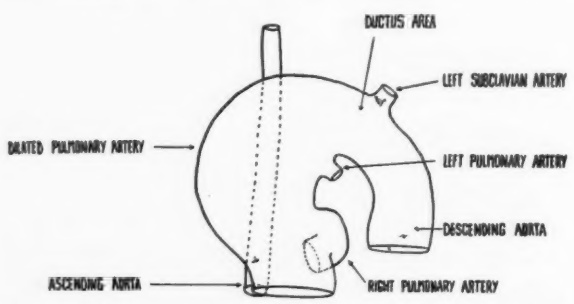


FIG. 4. Diagrammatic representation of the anomaly as seen at operation. Structures shown are in approximately correct size relationship.

COMMENTS

In the early human embryo there are two aortas—a dorsal and a ventral—which are connected by six paired arterial branches coursing through the mandibular and visceral arches. The direction of the circulation is ventral to dorsal through these paired vessels. The ventral aorta enters into the development of the heart while the dorsal vessel persists as the descending aorta. The paired connecting vessels are not all present at any one stage of development. The first three arches are well formed during the first month of embryonic life, as the fourth is just coming into being. By the six-week stage, the first and second arches have degenerated, and the third, fourth, fifth and sixth are present. Later, the fifth arch and part of the sixth also disappear. The third and fourth arches remain and enter into the formation of the aortic arch, carotid arteries and right subclavian artery. The remaining portion of the sixth arch enters into the formation of the pulmonary arteries, and a branch of the sixth arch forms the ductus arteriosus.[5,6] (Fig. 5.)

In this instance the defect occurred with failure of development, or the obliteration, of the fourth left arch the function of which was carried on by the pulmonary artery through a widely patent ductus arteriosus. This, in addition to failure of formation of the interventricular septum, is the defect under discussion.

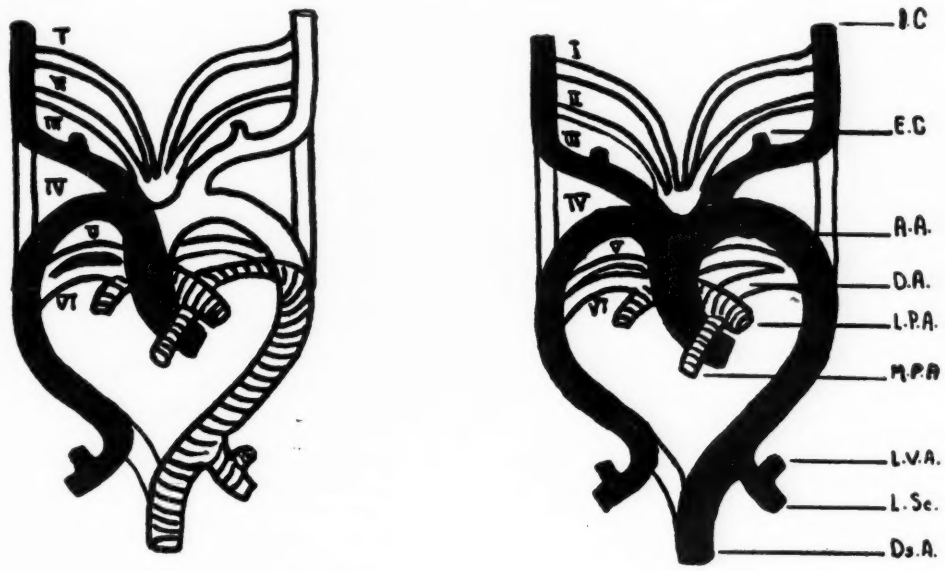
The aortic isthmus is quite narrow in the normal fetus so that most of the blood from the left ventricle goes into the vessels of the aortic arch. A large part of the right ventricular blood flows through the ductus arteriosus into the descending aorta. During fetal life, therefore, the lack of continuity between the ascending and descending aortas is of little significance. Pulmonary resistance at this time is probably equal to systemic resistance.

At birth, resistance in the pulmonary circuit declines as a negative intrathoracic pressure is established, while that in the systemic circuit rises; so that any shunt of blood in a patent ductus in the otherwise normal infant would be

from left to right after the first few days of life. At the same time, the right ventricle is exposed to a system of relatively lower pressure, and its work and muscle mass, compared to the left ventricle, decrease proportionately.

With failure of formation of the aortic arch, the fetal type of circulation is carried over into neonatal life, with a resultant increase in right ventricular work and compensatory changes in the pulmonary vasculature. The right ventricle must now force blood through the high resistance systemic circuit, and at the same time handle the greater part of the venous return from both right and left ventricular ejection, with resultant hypertrophy and dilatation. The pulmonary resistance rises to prevent flooding of the lungs, and compensatory pathologic changes occur in the pulmonary arteries and arterioles.[7,8]

Taussig[9,10] lists criteria for the diagnosis of patent ductus with reversal of flow which show striking similarity to the findings in this subject. These patients usually show right axis deviation or right ventricular hypertrophy on the electrocardiogram, a high-pitched blowing diastolic murmur along the left sternal border, an accentuated pulmonic second sound, and differential cyanosis of the upper and lower extremities. The possibility of slight cyanosis of the left hand due to proximity of the aortic end of the ductus to the left subclavian artery is mentioned, but neither Taussig nor Mendlowitz[11] describes differential clubbing of the hands due to congenital cardiac disease. The right brachial arterial oxygen content is normal, and the right femoral arterial oxygen content is decreased in varying degrees. The pulmonary arterial pressure is elevated, and the catheter may be passed through the ductus into the descending aorta. Angiocardiography shows simultaneous opacification of the aorta and pulmonary arteries.



5A 5B

FIG. 5. A, anomalous condition presented; B, normal development of circulatory system. I.C., internal carotid; E.C., external carotid; A.A., aortic arch; D.A., ductus arteriosus; L.P.A., left pulmonary artery; M.P.A., main pulmonary artery; L.V.A., left vertebral artery; L.Sc., left subclavian artery; Ds.A., descending aorta.

It is interesting that our patient fits these criteria exactly, with the exception of the angiocardiogram, which should have been diagnostic if available.

The preoperative opinion, therefore, on the basis of catheterization and physical findings, was patent ductus arteriosus with reversal of flow. It was believed also that we might be dealing with a fetal type of coarctation, despite the comparable pressures obtained in the arms and legs.

The increase of 4 cc./100 cc. in the blood O_2 content between the right atrium and the pulmonary artery was thought to represent either an interventricular septal defect or an intermittent left to right shunt from the aorta. Unfortunately, irritability of the right ventricle prevented us from obtaining a ventricular blood sample. After operation it was believed that, in

the absence of any evident source of oxygenated blood entering the pulmonary artery, this O_2 difference must have been due to an interventricular septal defect. It is the presence of this defect which we believe has enabled the child to survive to the present time, since it serves as a passage through which oxygenated blood may pass from the left side of the heart to the descending aorta. Since angiograms attempted via arterial and venous routes failed to visualize the area in question, an exploratory thoracotomy was decided upon.

On demonstration at operation of the anomalies present, the possibility of bridging the gap between the ascending and descending portions of the aorta with arterial grafts and ligation of the ductus was considered. It was believed, however, that this should not be attempted.

SUMMARY

This is a report of a case of unilateral clubbing of the fingers in a five year old Negro child due to absence of the aortic arch. The blood supply to the right upper extremity came through the aortic remnant while the left arm and the remainder of the body were supplied through a patent ductus arteriosus which opened widely into the descending aorta. Preoperative cardiac catheterization studies, roentgenograms of the heart with the catheter passing from the right ventricle into the descending aorta are presented in addition to the findings at operation. Consideration of the preoperative diagnostic possibilities and the embryology of the defect are included in the discussion.

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Complete Transposition of Great Vessels in a Male Aged Eighteen Years*

SIMAO PUNG, M.D., WERNER K. GOTTSTEIN, M.D. *and* EDWIN F. HIRSCH, M.D.
Chicago, Illinois

TRANSPOSITION of the great vessel trunks, an anomaly belonging to the cyanotic group of cardiac malformations, is rarely compatible with long survival, which is possible only if appropriate shunts exist. These shunts vary in location; and since they are of considerable physiologic interest, detailed descriptions should be made in every individual case. The case herein described is unusual because of the long period of observation and the severity and complexity of the patient's symptoms.

CASE REPORT

This white male was under clinical observation at the Children's Memorial Hospital in Chicago from May, 1938 (aged three years, one month) until March, 1948 (aged twelve years, eleven months) and at St. Luke's Hospital, Chicago, from October, 1948 (aged thirteen years, six months) until his death on December 2, 1953 (aged eighteen years, eight months).

In 1938 the mother brought the boy, aged three years, to the Clinic because he did not walk and was getting about only in a walking chair. She knew that this boy, in contrast to two healthy siblings, was a "blue baby." He had had fainting spells two days after his birth and she had been told that he had "heart trouble" when he was two weeks old. He became extremely cyanotic on crying, was always thin, and did not sit without support until he was eighteen months old. When first examined he had signs of general underdevelopment despite a fairly good nutrition. His weight at the age of three years was 24 pounds (average 32 pounds), his height 34 inches (average 38 inches). There was deep cyanosis of the entire skin, more pronounced of the lips, the tongue and the oral mucosa. The apex beat was midway between the left midclavicular and the anterior axillary line. There was a pronounced systolic thrill and the loudest systolic murmur was in the region of the third or fourth rib at the left sternocostal border, though widely transmitted as far as the left axilla. Some of these external clinical signs changed slightly during the observation period of fifteen and one-half years, some increased, and some fluctuated. Cyanosis of the skin, conjunctivae and mucous membranes, and the clubbing of fingers and toes were almost the same throughout the entire period, though more conspicuous during the last three months of the patient's life when the pulmonary manifestations coincided with a rather rapid decline in his general condition.

The degree of compensatory polycythemia remained stationary between 19 and 22 gm. hemoglobin and 7,000,000 and 9,000,000 erythrocytes per cu. mm. It is remarkable that the hemoglobin became as high as 25 gm. per cent at the age of ten years, and that it was only 15.8 gm. per cent (erythrocytes 5,800,000) five days prior to his death because of the progressive peripheral edema. The somatic habitus developed as he grew older though normal maturation failed to appear. There was more frontal bossing of the skull and greater prominence of the left side of the chest. Retardation of physical development became more marked with the onset of adolescence. At the age of eighteen years he had the physical and psychologic habitus of a boy aged twelve years. There were no changes in the voice nor was there maturation of secondary sexual characteristics. The manifestations of cardiac decompensation fluctuated. Between the third and seventh years the liver was almost constantly enlarged. Between the thirteenth and seventeenth years there were periods of diffuse rales in the chest, hacking cough and marked dyspnea in a recumbent position, which alternated with periods of relatively good compensation. Even in the later years, and despite

* From the Henry Baird Favill Laboratory and the Cardiac Clinic of St. Luke's Hospital, Chicago, Ill.

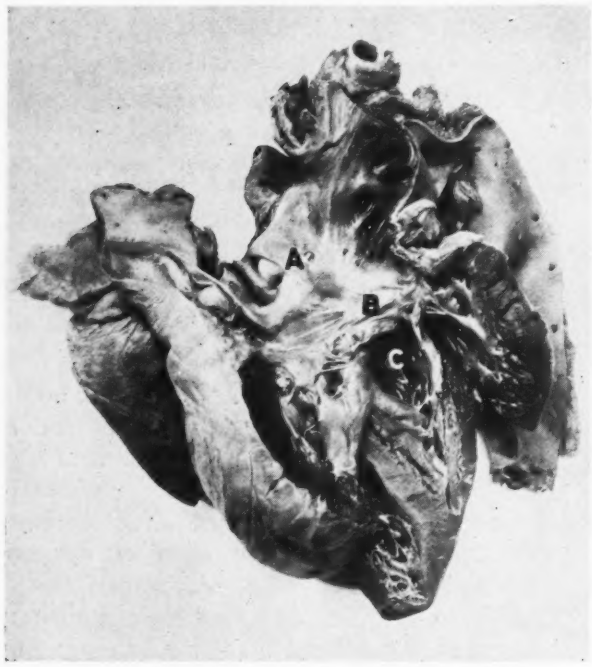

FIG. 1. Photograph of the right side of the heart illustrating the widely patent foramen ovale (A), the tricuspid ring (B), the ventricular recess (C) and the marked hypertrophy of the myocardium of the right ventricle.

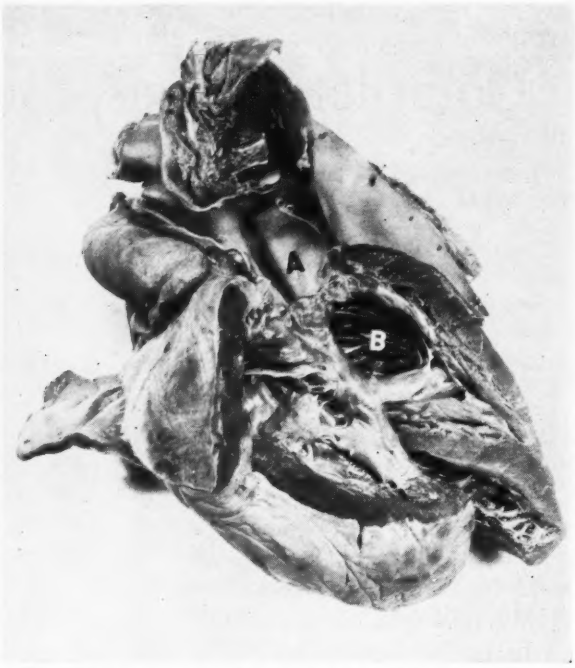

FIG. 2. Photograph of the right side of the heart illustrating the origin of the aorta (A) in the ventricle, the ventricular recess (B) and the marked hypertrophy of the myocardium.

cardiac distress, he did not miss one of his monthly appointments, travelling sixty-five blocks without squatting to rest. Digitalis maintenance doses were the only medication. At the age of fifteen years his resting arterial saturation was 65 per cent. After five minutes of light exercise, walking on a treadmill at two miles an hour, the saturation dropped to 27 per cent but quickly returned to its base line after a few minutes of rest. (Tests by Dr. Donald E. Cassels, Department of Pediatrics, University of Chicago.) Prior to death the correct diagnosis was suggested several times but never established with certainty. Roentgen examinations, electrocardiogram and angiocardiogram studies pointed to various cardiac malformations of the cyanotic type. Combined fluoroscopy and film studies showed enlargement of the right and left ventricles but no enlargement of the left auricle, and absence of the pulmonary conus. The lung fields revealed a marked increase of the peribronchial markings. On the basis of these observations the tetralogy of Fallot with increased vascularity and congestion of the lung fields was diagnosed. Repeated electrocardiograms showed left heart preponderance, considered to be suggestive of tricuspid atresia in the cyanotic type, though not compatible with survival beyond early childhood. Finally, the angiocardiogram suggested a third possibility: "Following injection of about 30 cc. of neoiopax,® the venous inflow into the heart was readily demonstrated. The right auricle filled quickly, also the right ventricle filled. Arising from this, the aorta immediately filled and the arch and descending aorta visualized unusually well. There was no suggestion of any vessel coming off the ventricular mass which could be interpreted as representing a pulmonary artery. It seems quite clear that the aorta fills from both the right and left ventricles, that there is no pulmonary artery, and that the pulmonary vascular tree fills from tributaries of the aorta, presumably bronchial arteries. Therefore, the most probable diagnosis is truncus arteriosus communis, with the pulmonary supply arising from bronchial arteries." The angiocardiogram was performed when the patient was fifteen years old but his general condition made cardiac catherization inadvisable at that time.

The decline of the patient began in September, 1953, three months prior to his death, with diffuse edema of the legs, more dyspnea on slight physical exertion, increasing distention of the abdomen, persistent cough, elevation of the temperature and a metastatic osteomyelitis of

the right sternoclavicular joint secondary to pulmonary abscesses.

The significant findings at necropsy were as follows: Most of the heart was a cone-shaped mass of ventricular muscle tissue 10 cm. long and at the base 9.5 by 8 cm. The tip was bluntly rounded. The aorta was in front and arose from the right ventricle. The pulmonary artery was behind the aorta on the left side. The outside diameter of the aorta was about 2.5 cm. and directly behind it was the pulmonary artery. When the heart was opened to expose the right auricle into which the superior and the inferior venae cavae drain, a misshapen ventricle structure that curved around in front of the root of the aorta was exposed. (Figs. 1 and 2.) The lining of the right auricle, auricular appendage and the ventricle was slightly thickened by fibrous tissue. The circumference of the tricuspid ring was 8.5 cm. The leaflets were thickened at their free margins by fibrous tissues. (Figure 1B.) The misshapen right ventricle measured from the attachment of the tricuspid ring to the apex was 5 cm. and from the aortic ring to the apex 5.5 cm. The wall of the right ventricle was markedly hypertrophied; measured along the septum in front, at the aortic ring level, it was 1.1 cm. Just below the aortic ring, medially, the interventricular septum presented a deep excavation, 3 by 2 cm. and about 2.5 cm. deep. (Figs. 1C and 2B.) This did not communicate with the left ventricle. The aortic ring was 5 cm. in circumference. (Fig. 2A.) The semilunar valves were thin. The sinuses of Valsalva were deep. The usual three cusps were present but the right and left cusps were situated posteriorly and the posterior cusp was in front. The mouth of each coronary artery was widely patent and corresponded to the right and left cusps. However, because of the transposition of the great vessels, the left coronary artery was now on the right side and the right coronary artery was on the left. The ductus arteriosus was closed. The foramen ovale was widely patent (Fig. 1A), 2.5 cm. in its greatest diameter. Upon opening the left ventricle posterolaterally, the endothelial lining of the left auricle, auricular appendage and left ventricle were found to be slightly thickened. The circumference of the mitral ring was 6 cm. The leaflets were thickened by small fibrous nodules less than 1 mm. in diameter, some of them calcified. The pulmonary artery connected (Fig. 3A) with the left ventricle through a fibrous ring in the conus (Fig. 3B)

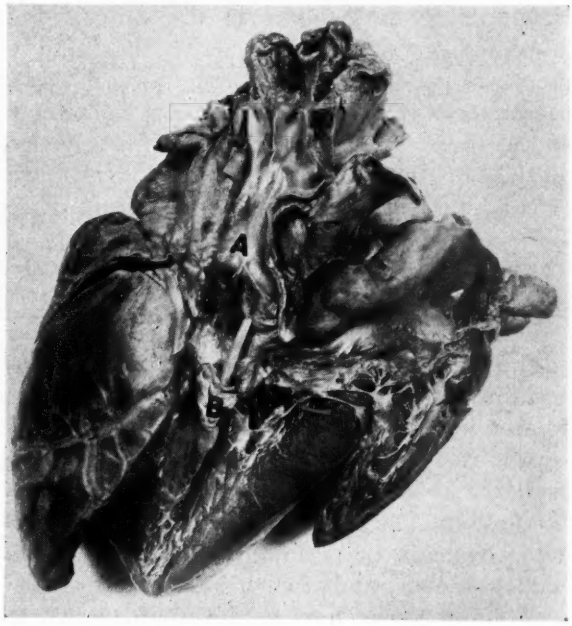

FIG. 3. Photograph illustrating the left side of the heart with the pulmonary artery (A) arising from the left ventricle. In the infundibulum (B) is the fibrous stricture through which a probe is inserted.

surrounded by calcified nodules. The lumen here was narrowed to about 15 mm. in diameter. This stricture (Fig. 3B) was at the level of and anterior to the mitral ring and 2 cm. below the attachment of the pulmonic leaflets, thus representing an infundibular structure. The wall of the left ventricle was hypertrophied. Measured anteriorly, the thickness of the wall was 1.3 cm. near the apex.

Portions of each pleural space were obliterated by fibrous adhesions and both lungs had many focal abscesses that ranged to several centimeters in diameter. Each pleural space contained about 800 cc. of a clear limpid fluid. The spine had a marked S-shaped curvature. At the sternal end of the right clavicle was an abscess 5 cm. in diameter. The bone here was markedly eroded. A mixed growth of bacteria grew out in cultures of the exudates. The kidneys, liver and spleen showed the changes of marked chronic passive hyperemia. The cortex of the bones was thin but there was a large amount of dark red spongiosa, so firm in texture as to suggest osteosclerosis.

The final anatomic diagnosis was: complete transposition of the aorta and pulmonary artery with closed ventricular septum and ductus Botalli, but with widely patent foramen ovale and calcified stenosis of the pulmonary conus of the left ventricle; fibrous changes with cal-

cification of the leaflets of the mitral ring; dilatation of the chambers and hypertrophy of the myocardium of the heart; marked hypertrophic osteoarthropathy of the distal phalanges of the fingers and of the toes; chronic osteomyelitis of the right clavicle; multiple abscesses of the lungs; chronic passive hyperemia of the kidneys, spleen and liver.

COMMENTS

The pathologic physiology of complete transposition of the great vessels has been discussed in detail by Taussig[1] and by P. D. White.[2] Survival beyond early infancy is possible only if shunts are available that permit the crossing of the two circulations. The greater the volume of the shunt, the greater is the admixture of arterial and venous blood, and the less is the cyanosis. Cooley and Sloan[3] have analyzed fifty-two cases described in more recent publications, thirteen of these cases having been verified by autopsy. These authors differentiated the available shunts by angiographic examination. In a number of cases it was possible to determine with accuracy whether the shunting of arterial and venous blood was provided by (1) an interatrial septal defect, (2) an interventricular septal defect, (3) a patent foramen ovale and interventricular septal defect, (4) a patent ductus arteriosus and interventricular septal defect and (5) a patent foramen ovale, patent ductus arteriosus and interatrial septal defect. Among the single defects interventricular septal defect was associated with the longest life span. However, a combination of interventricular septal defect and patent foramen ovale permitted even longer duration of life. Obviously, the presence of two shunts prevented unidirectional flow and avoided stagnation of blood in the greater or lesser circulation. Such shunts explain the relative longevity of these cases. The reviews of Cooley and Sloan as well as those of Hanlon and Blalock[4] have shown that patients with transposition may live longer than the usual maximum of eighteen months. Nevertheless, in these larger series a life span of eight to ten years was exceptional.

Occasional observations record a much longer survival. Messeloff and Weaver[5] described transposition of the great vessels in a Negress who reached the age of thirty-eight years. The clinical observation period was short because the patient was in the hospital for only a short time before she died. She had had some degree of cyanosis since childhood but the onset of circulatory failure came just before hospital admission. The autopsy demonstrated not less than three compensatory mechanisms explaining such long survival: (1) a large interventricular septal defect; (2) a patent foramen ovale and (3) two aberrant pulmonary veins that entered the right atrium. A similar multifactor compensation was present in the case of Carns, Richie and Musser[6] who described transposition of the great vessels in a woman aged forty-four years. In this heart there was such a huge defect of the interventricular septum that the heart functioned as a cor biatriatum triloculare. Moreover, there was dextroposition of the transposed pulmonary artery and a patent foramen ovale.

In contrast with these examples, the heart of our eighteen year old male showed a rather unsatisfactory compensation mechanism in regard to shunts. The only communication permitting crossing of the two circulations was a foramen ovale of 2.5 cm. in diameter. Even those patients whose transposition was associated with two shunts seldom reached the age of eighteen years. Obviously, relative longevity depends not only on mechanical factors, such as the diameter of shunts, but also on biologic conditions that cannot be evaluated fully. Two such factors might be considered. The first is a gradual adaptation to a tolerable deficiency of oxygen supply. Experience with all forms of cyanotic heart disorders indicates that children adjust themselves to cyanosis, at least to a certain extent. The second factor is the retardation of growth and development which may operate as a biologic defense mechanism. During the entire fifteen years of observation of this patient less weight increase remained below the 25 percentiles of the standard values. With the onset of puberty, there was almost complete abeyance of development. This might be considered, in a way as a self-preserving cessation of growth.

In many cases of congenital malformations of the heart, death is not caused by the anomaly itself but by secondary intracardiac and extracardiac changes. In our case, three main factors were responsible: (1) gradual increase of the pulmonary stenosis by progressive fibrosis and calcification in the conus; (2) interstitial changes in the lungs and (3) loss of resistance to infection leading to pulmonary abscesses and osteomyelitis.

SUMMARY

The case of an eighteen year old male with transposition of the great vessels is described. The only available shunt that rendered possible the crossing of the two circulations was a widely patent foramen ovale. In previous communications such relative longevity in cases of transposition of the great vessels has been observed in cases only with larger and multiple shunts.

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Aortic Sinus Aneurysm*

Production of Intracardiac Calcification and Pulmonary Artery Fistula

JOSEPH C. SHIPP, M.D., LEONARD V. CROWLEY, M.D. *and* RUSSELL WIGH, M.D.

Boston, Massachusetts *Columbus, Ohio* *New York, New York*

SYPHILITIC aneurysms of the thoracic aorta are relatively common and usually can be visualized roentgenologically. However, syphilitic aneurysms involving the aortic sinuses (sinuses of Valsalva) are rare. Jones and Langley[1] collected forty-seven cases of sinus aneurysm. The majority of these were congenital. Only seventeen were of syphilitic origin.

Most aortic sinus aneurysms are small and cannot be detected by conventional roentgenologic methods. Since these aneurysms frequently project into the cardiac chambers, they may lie within the mediastinal shadow. The changes that occur in the cardiac silhouette will depend on the size of the aneurysm and the sinus from which the aneurysm arises. A sinus aneurysm may expand posteriorly and encroach on the left atrium, simulating an enlarged left atrium. Kerley[2] cites a case in which an aneurysm was suspected clinically. However, radiologic examination revealed an apparently enlarged left atrium which displaced the esophagus posteriorly. The autopsy revealed that the apparent atrial enlargement was the result of a sinus aneurysm projecting into the atrial chamber. Ostrum[3] described a sinus aneurysm that bulged into the left atrium and reduced the capacity of that chamber. The aneurysm also produced a cardiac silhouette similar to that seen in mitral stenosis.

Syphilitic aneurysms frequently cause death as a result of rupture into the pericardial or pleural spaces. However, rupture of an aortic aneurysm into the pulmonary artery is uncommon. The reported incidences range from 3.7 per cent to 1.8 per cent.[4–6] In the Presbyterian Hospital autopsy series this complication had not been seen previously in 114 cases of thoracic aneurysm, of which forty-two had ruptured. Since Nicholson's review[6] covering eighty-three cases of aortic aneurysm arising from various sites and rupturing into the pulmonary artery, three additional cases have been reported in the American literature.[7–9] In two recent cases[8,9] cardiac catheterization studies aided in establishing the diagnosis.

The development of a fistula between an aortic aneurysm and the pulmonary artery is accompanied by a well established clinical syndrome.[6,7,10] This is characterized by the sudden onset of marked dyspnea which is usually associated with systolic and diastolic cardiac murmurs, precordial thrill, wide pulse pressure and evidence of right ventricular failure. An aortic-pulmonary artery fistula is usually compatible with life for a period of a few weeks to several months.[6,8] Such a communication will cause dilation of the pulmonary artery because of the increased pulmonary blood flow and increased pulmonary artery pressure. The enlarged pulmonary artery can be demonstrated radiologically.

The following case of an unusual syphilitic aortic sinus aneurysm is reported not only because of its rupture into the pulmonary artery but also because its position and the calcification of its wall simulated an enlarged left atrium roentgenologically.

CASE REPORT

The patient (Unit No. 167284), a fifty-two year old Dominican Republic tailor, was admitted to Presbyterian Hospital on December 27, 1953, because of severe dyspnea of two weeks' duration.

The family history indicated that the patient's mother and brother had died of tuberculosis. In his youth the patient had had gonorrhea and chancroid. There was an equivocal history of syphilis. He had never received any specific

* From the Departments of Medicine, Pathology and Radiology, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital, New York, N. Y.

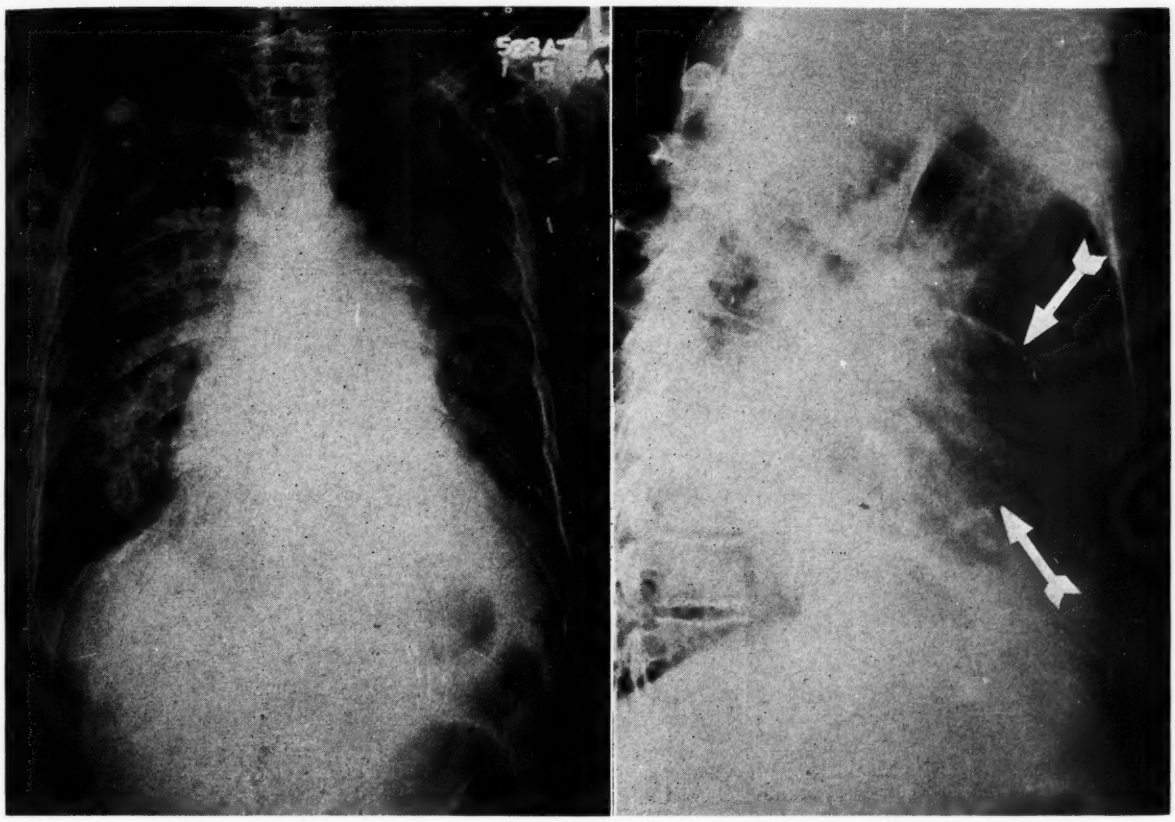

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FIG. 1. Postero-anterior roentgenogram of the chest demonstrating cardiac enlargement with a prominent, convex pulmonary artery segment. The bilateral pulmonary densities represent inflammatory and congestive changes.

FIG. 2. Lateral chest roentgenogram demonstrating a ring of calcium (arrows) within the cardiac contour (posterior aspect of ring concealed by pulmonary densities).

antisyphilitic therapy. However, at the age of forty-six he had received a three-week course of penicillin for "pneumonia." Mild asthma had been present for the past fifteen years. There was no history suggestive of congenital or rheumatic heart disease.

In 1945 and 1947 he was informed of a cardiac abnormality. For the past six years he had experienced slowly progressive exertional dyspnea and episodes of wheezing with an associated cough productive of mucopurulent sputum. Two weeks before admission he noted the sudden onset of marked dyspnea, orthopnea, chills and fever. The chills and fever subsided coincidentally with penicillin therapy. However, the extreme dyspnea and orthopnea persisted. He entered another hospital where a diagnosis of decompensated syphilitic heart disease was made. He was treated with digoxin, mercuhydrin, oxygen and aureomycin, without significant response. He left the hospital against advice on December 25, 1953. However, dyspnea became more marked and he entered the Presbyterian Hospital two days later.

The admission physical examination revealed a temperature of 98.8°F., pulse 128, respirations 40 and blood pressure 150/50. The patient was well developed. However, he appeared chronically ill and showed evidence of recent weight loss. He was in acute respiratory distress and was slightly cyanotic. Pupils and fundi were normal. There was no tracheal tug or tracheal deviation. The neck veins were not distended and the venous pressure was 100 mm. of water. There were rales and rhonchi throughout both lower lung fields, with evidence of fluid at the left base. The heart was enlarged to the anterior axillary line. Cardiac rhythm was regular. There was a continuous thrill, and a loud continuous systolic and diastolic murmur heard over the entire precordium. The murmur had a machinery-like quality, was of maximum intensity to the left of the sternum in the second and third interspaces, and was transmitted into

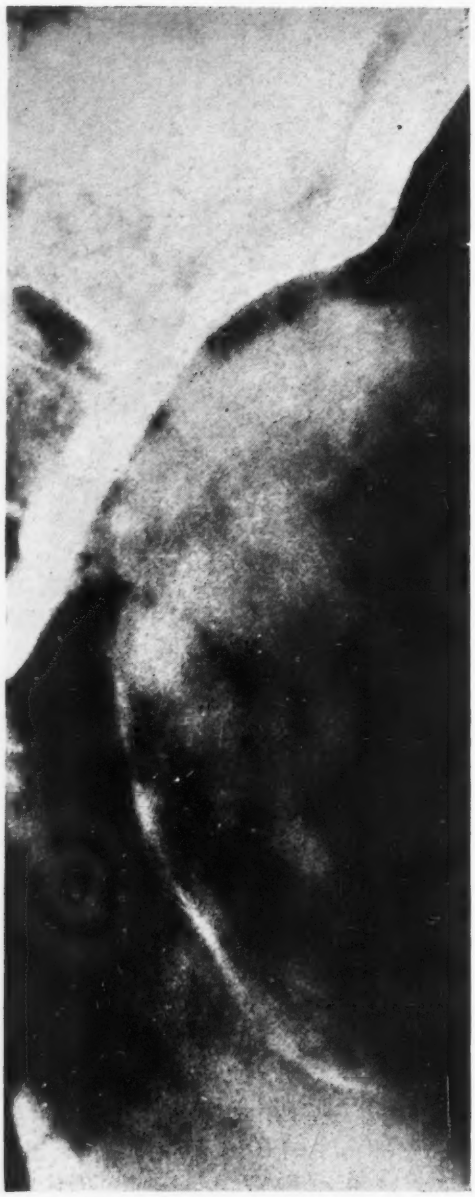


FIG. 3. Spot roentgenoscopic exposure in the right anterior oblique projection showing the barium-filled esophagus displaced posteriorly. The calcified portion of the aneurysm is in close proximity to the esophagus.

the neck, axilla and back. The aortic second sound was of good quality and louder than the second pulmonic sound. Apical heart sounds were thought to be normal. The pulse was Corrigan in type. The liver and spleen were not palpable. There was no edema or clubbing. Embolic manifestations were not present.

Laboratory studies revealed a hemoglobin of 15 gm. per 100 ml., leukocyte count of 12,000 per cu. mm. with an essentially normal differential, sedimentation rate (Westergren) of 24 mm. in one hour, blood urea nitrogen 34 mg. per cent, and serum carbon dioxide 34 mEq./L. Serologic tests for syphilis included: Kolmer 3+, Mazzini negative and VDRL negative. The treponemal immobilization test (with penicillinase) was "non-specific." The fasting blood sugar, serum albumin and serum globulin were within normal limits. The cephalin flocculation and thymol turbidity tests were negative. The urine and stool were normal. Repeated blood cultures and sputum studies revealed nothing of significance. Numerous sputum examinations for tubercle bacilli were negative, and the tuberculin test was negative at 1:1000 dilution. Fluid from the left pleural space had the characteristics of a transudate and was negative on culture and cell block examination. Electrocardiograms showed slight right axis deviation, non-specific changes of myocardial damage and abnormal P waves suggestive of atrial disease.

Radiologic studies, including roentgenoscopy, demonstrated an enlarged heart with a very prominent convex pulmonary artery segment. (Fig. 1.) A thin ring of calcium was seen within the cardiac silhouette. (Fig. 2.) This annular shadow, which displaced the esophagus posteriorly (Fig. 3) and to the right, was interpreted as an enlarged, calcified left atrium. The ascending aorta was not dilated or calcified. There was a fan-shaped density in the right lung field, spreading peripherally from the hilum. Some increased density at the left lung base was partially obscured by fluid.

The patient was treated with digitoxin, mercurial diuretics, rigid salt restriction, oxygen and penicillin. Streptomycin and isonicotinic hydrazide were added subsequently because of the possibility of subacute bacterial endocarditis or tuberculosis. There was no significant response to therapy. Roentgenologically, there were only minor variations in the pulmonary densities and pleural fluid. The patient remained afebrile. Marked dyspnea and cyanosis continued, and he died on the twenty-fifth hospital day.

Pathologic Anatomy. Significant autopsy findings were limited to the heart, aorta and lungs. Before describing these in detail, it is necessary to call attention to the fact that there are several systems of nomenclature currently used in designating the aortic sinuses and related valve cusps. We prefer to follow the recent trend, naming the sinuses and valve cusps in relation to the coronary arteries. Thus the left aortic sinus is that sinus giving origin to the left coronary

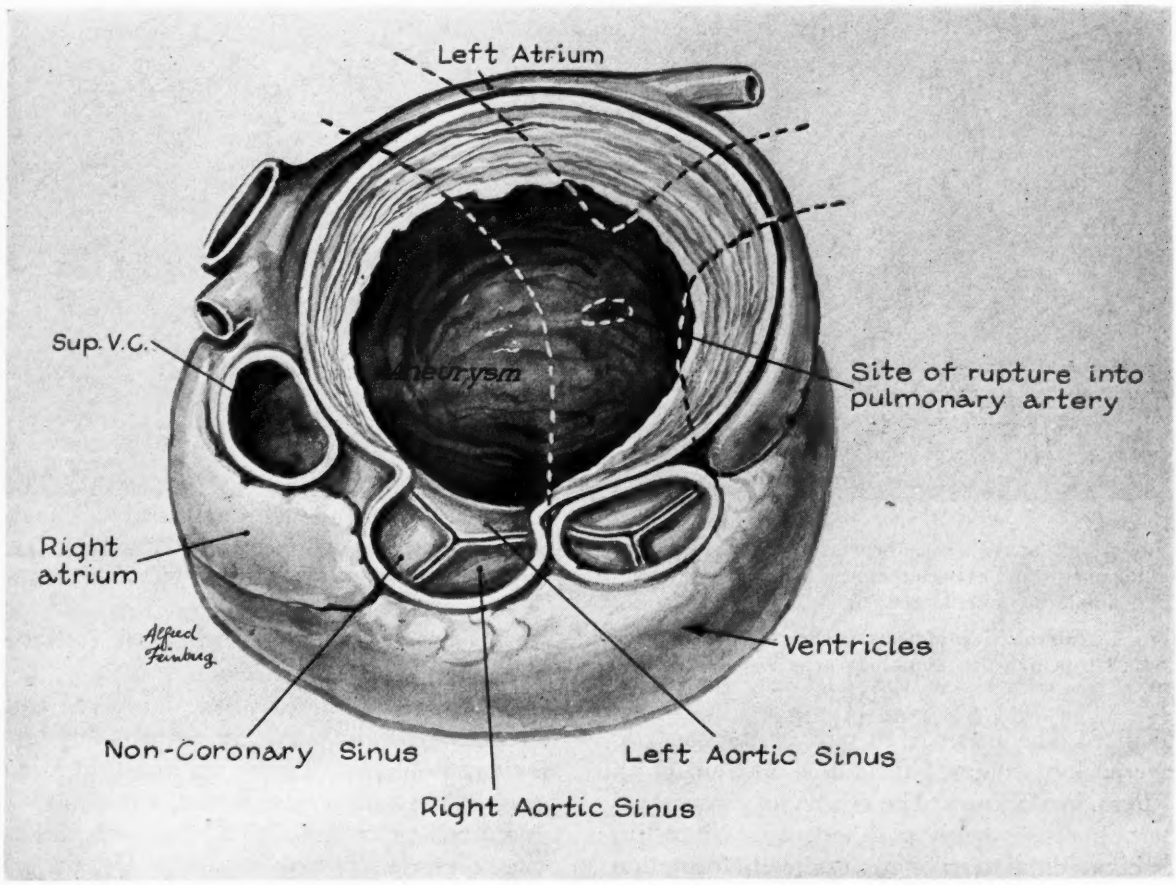


FIG. 4. The heart viewed from above, showing compression and displacement of the left atrium and auricular appendage by the aneurysm. The upper half of the aneurysm has been removed. The pulmonary artery and site of fistula are represented by dotted lines.

artery; the right aortic sinus gives origin to the right coronary artery. The third sinus has no coronary ostium; accordingly, it is designated the non-coronary sinus, as suggested by recent authors.[1] Employing this terminology, the aneurysm in this case arose from the left aortic sinus. This sinus has also been called the left anterior, left posterior or left lateral sinus. Figure 4 illustrates semidiagrammatically the abnormal anatomic features and is labelled using the system of nomenclature suggested.

The cardiac configuration was abnormal, due to the presence of a large saccular aneurysm measuring approximately 9 cm. in all diameters. The aneurysm arose from the left aortic sinus and adjacent ascending aorta. It had expanded posteriorly and laterally to encroach on the left atrium and auricular appendage. (Fig. 6.) The aneurysm was partially intracardiac, and did not project above the base of the heart to any appreciable extent. The aortic orifice of the sac measured approximately 3 by 5 cm. The superficial part of the aneurysm wall was irregularly

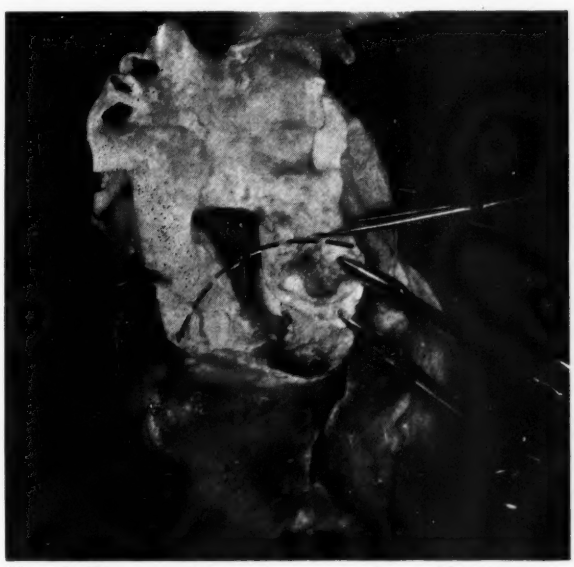
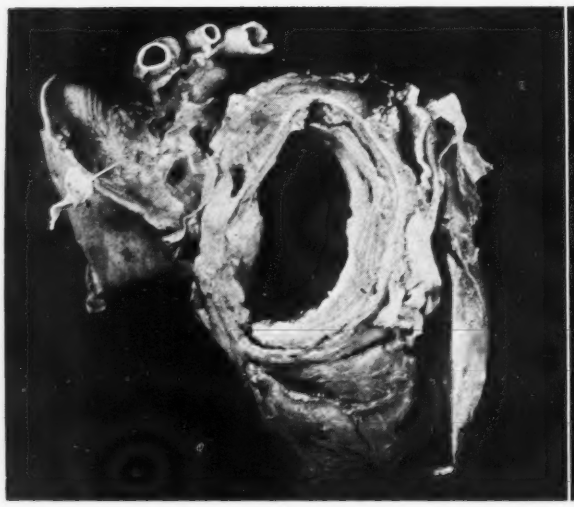


FIG. 5. Photograph showing ventricles, orifice of aneurysmal sac, and scarred ascending aorta. The dotted line represents the approximate position of the aortic ring. The aneurysm arises in part from the left aortic sinus (below dotted line) and in part from the adjacent ascending aorta.



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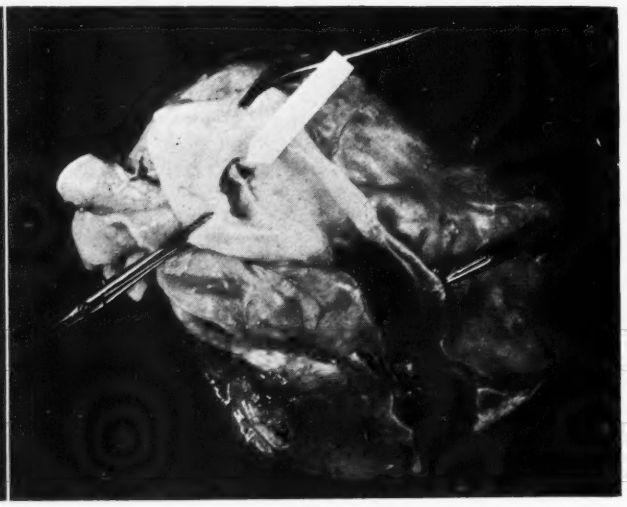

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FIG. 6. Left lateral view of heart, showing aneurysm above and lateral wall of left ventricle below. The lateral wall of the aneurysm has been removed. The sac has flattened out the left atrium and occupies the position of this chamber, simulating an enlarged left atrium.

FIG. 7. Anterior view of heart. Hypertrophied right ventricle and pulmonary artery have been opened. The aneurysm lies behind the pulmonary artery. Arrow indicates site of the fistula.

calcified. The internal surface of the sac was covered by laminated thrombus, measuring up to 2 cm. in thickness. The aneurysm compressed the pulmonary artery and had eroded into this vessel proximal to its bifurcation, with formation of a fistula between the sac and the pulmonary artery. The opening of the fistula measured 0.6 cm. in diameter. (Fig. 7.)

The combined weight of the heart and aneurysm was 675 gm. Much of this increase in weight was due to the aneurysm. The left ventricle was only slightly hypertrophied, measuring 1.6 cm. in thickness. However, the right ventricle was markedly hypertrophied, measuring 1.0 cm. in thickness.

There was some sagging of the left cusp of the aortic valve; the other cardiac valves were normal. Both coronary arteries showed only slight atheromatous change and were widely patent.

The ascending aorta was scarred, having the gross appearance of syphilitic aortitis. The scarring extended into the aortic sinuses but did not narrow the ostium of the right coronary artery. Microscopic examination of the ascending aorta revealed vascularization of the media associated with patchy scarring and destruction of elastic fibers. These histologic features were also consistent with syphilitic aortitis.

The aneurysm also compressed the main bronchi. The left lung was of normal weight but was partially atelectatic, probably as a result of bronchial obstruction due to the compression and excessive bronchial secretions.

Microscopic examination revealed extreme congestion, patchy atelectasis and slight pulmonary fibrosis. The right lung was much heavier than normal, weighing 950 gm. All lobes were consolidated. Histologically, in addition to the changes of extreme chronic pulmonary congestion there was a superimposed organizing pneumonia involving all lobes of this lung.

COMMENTS

Clinically, the patient's dyspnea and pulmonary congestion were interpreted as evidence of cardiac failure. Although the etiology was uncertain, the past history of venereal disease, the positive serologic test for syphilis and the basal murmurs strongly suggested syphilitic cardiovascular disease with the formation of an aneurysm with aortic insufficiency. The sudden onset of symptoms, the intractable course and the continuous murmur raised the question of rupture of an aortic aneurysm into the pulmonary artery. However, the inability to demonstrate aortic dilation roentgenologically made this latter possibility seem less tenable. A patent ductus arteriosus, with superimposed bacterial arteritis and pulmonary embolization, was considered because of the continuous mur-

mur, prominent pulmonary artery and multiple pulmonary densities. Mitral valve disease was implicated because of the prominent pulmonary artery and apparent left atrial enlargement. It was thought that co-existing rheumatic aortic valve lesions might explain the basal murmurs.

In this case, the apparent left atrial calcification was believed to be strongly suggestive of mitral valve disease, since it is generally considered that calcification within the left atrium is secondary to rheumatic heart disease. Indeed, although the literature includes reports of aortic sinus aneurysm with compression of the left atrium,[2,3] there is no mention of the roentgenologic demonstration of calcification in the atrial position from this cause. In a consideration of the differential diagnosis of atrial calcification, recent authors[11] include calcification involving coronary arteries, ventricular aneurysms, mitral and aortic valves, pericardium, echinococcus cysts and cardiac tumors. No mention is made of the possibility of a calcified aortic aneurysm in the left atrial position. Some recent illustrations of left atrial calcification associated with mitral stenosis[12] demonstrate roentgenologic findings almost identical with those in this case. If this patient had been in less critical condition, more definitive studies, including angiocardiography and cardiac catheterization, would probably have aided in establishing the exact diagnosis.

This patient's acute episode, occurring about six weeks prior to death, probably indicated the development of the pulmonary artery fistula. According to Porter[7] the severe dyspnea is referable to an exaggerated Hering-Breuer reflex resulting from the marked engorgement of the pulmonary vascular bed. Some degree of left ventricular failure may have been a contributory factor in the present case.

Although there was no clinical evidence of right heart failure, there was a significant degree of right ventricular hypertrophy. Probably several factors were responsible. Some hypertrophy was a direct consequence of the aortic-pulmonary artery shunt. However, compression of the pulmonary artery by an aneurysm, even without fistula formation, may produce similar changes.[13] Other factors are more difficult to evaluate. The invagination of the aneurysm into the left atrium would be expected to reduce the capacity of this chamber and might also impede pulmonary venous return. These abnormalities would tend to cause pulmonary congestion, pulmonary hypertension and compensatory right ventricular hypertrophy.

The pneumonia in the right lung was an additional factor in causing the patient's death. The intense pulmonary congestion probably predisposed to the bacterial infection. Bronchial compression by the aneurysm, with retention of bronchial secretions, may also have contributed to the development of the pneumonia and its resistance to treatment.

CONCLUSIONS

A case of an unusual syphilitic aneurysm involving the left aortic sinus is presented. Rupture of the aneurysm into the pulmonary artery produced a clinical syndrome characterized by the sudden onset of severe dyspnea associated with physical findings of an aortic-pulmonary artery fistula.

An aortic sinus aneurysm that protrudes into the left atrium may produce a roentgen configuration similar to that seen in rheumatic mitral valve disease. Even the occurrence of calcification in the wall of such an aneurysm may simulate the atrial calcification occasionally seen in rheumatic heart disease.

In the absence of known congenital or rheumatic heart disease, such findings in a patient with syphilis should be considered strongly suggestive of syphilitic cardiovascular disease.

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Pasteurella Multocida Septicemia in Man*

A. G. Bearn, M.D., Katia Jacobs, B.S. *and* Maclyn McCarty, M.D.
New York, New York

Although not very uncommon in certain animals, Pasteurella multocida infections are rare in man and worthy of recording. An organism indistinguishable from P. multocida was isolated from the blood of a young woman with cirrhosis of the liver upon whom a splenorenal shunt had been performed five years previously. This organism was also isolated from the throat of the patient's pet cat.

CASE REPORT

The patient was a twenty-five year old, single, white woman who at the age of twelve developed an attack of acute hepatitis. A severe esophageal hemorrhage two years later proclaimed the development of posthepatitis cirrhosis. Further episodes of hemorrhage followed, which occasionally precipitated periods of hepatic coma and the formation of ascites. In 1947, three years after the first hemorrhage, a splenorenal shunt was successfully performed. Following the shunt operation no further hemorrhage occurred and her ascites promptly disappeared. A persistently low concentration of albumin in the serum resulted in the appearance of intractable edema of her extremities.

Three weeks prior to admission the patient developed a severe shaking chill and her temperature rose to 103°F. She was given penicillin and terramycin.® Her temperature returned to normal by the next day and although she felt somewhat weak she was able to return to work. A few days later another shaking chill occurred but improved within twenty-four hours, this time without the administration of antibiotics. A week later she experienced a further severe shaking chill and her temperature again rose sharply. She was admitted to The Hospital of The Rockefeller Institute on the same day. Examination revealed a sick girl with puffiness of the face, temperature 103°F., pulse 112, respirations 28. Clinical examination did not disclose any localizing signs or symptoms. The physical signs referable to cirrhosis of the liver had not changed since she was seen in the Outpatient Clinic a month previously. A series of healed scratch marks resulting from scratches from her pet cat were visible on her face and extremities.

Chest x-ray was normal. The white count was 24,000; polymorphonuclear leukocytes 88 per cent. The total serum protein was 4.7 gm. per cent; serum albumin 1.1 gm. per cent; bilirubin 3.6 mg. per cent; zinc turbidity test 24 units. The severity of the hepatic cirrhosis and the danger that prolonged fever might precipitate hepatic coma prompted immediate administration of antibiotics without waiting for the results of bacteriologic findings. Treatment with procaine penicillin, 300,000 units intramuscularly b.i.d., and streptomycin, 1 gm. q.d., was initiated and continued for five days. Within twenty-four hours her temperature was normal and she felt improved. The temperature remained normal for the remainder of her hospital admission. After five days her white count had fallen to 7,000. She felt well and was allowed to return home.

Bacteriologic Findings. A blood culture taken on the day of admission showed heavy growth in broth and there were innumerable colonies in the agar pour-plates containing 1 ml. of blood. Microscopic examination of stained smears revealed tiny gram-negative organisms, coccobacillary in form, that showed some tendency to bipolar staining. The organism grew readily on complex media (beef-heart infusion with neopeptone) and on agar surfaces formed gray, butyrous, glistening colonies that resembled E. coli. However, there was no growth on media used for differentiation of enteric gram-negative organisms (eosin-methylene blue agar, desoxycholate-citrate agar).

Further bacteriologic examination yielded the following results: The organism was non-motile. It fermented dextrose, sucrose and trehalose weakly with the formation of acid but not of gas. Lactose, maltose and xylose were not fermented.

* From the Hospital of The Rockefeller Institute for Medical Research, New York, N. Y.

Tests for the formation of indol and the production of nitrites from nitrates were strongly positive; and the test for H_2S production was weakly positive. Hemolysis was not produced on blood agar. It did not liquefy gelatin or alter the reaction of litmus milk. The growth of the organism was completely inhibited by penicillin at a concentration of 0.75 units per ml., and only slight growth occurred at 0.3 units per ml. It was virulent for mice when injected into the peritoneal cavity.

These findings indicate that the organism belongs to the genus Pasteurella and is closely similar to those strains designated as P. multocida. Because of the common association of Pasteurella infections with animal bites, an inquiry was made into the possible animal contacts the patient may have had. The patient had been bitten and scratched by her pet cat shortly before the onset of her illness and cultures were obtained from this animal. A gram-negative organism resembling that obtained from the patient's blood was isolated from the cat's throat. It proved to be identical in growth properties, fermentation and biochemical reactions, penicillin sensitivity and mouse virulence. Thus there is presumptive evidence that the cat was the source of the infecting bacterium.

COMMENT

From a study of the literature it is apparent that human infection with P. multocida is often caused by contact with an infected cat. Schiffer[1] in his review described thirteen cases in which the source of the infecting agent was known with reasonable certainty. Of these six (46 per cent) were presumed to be the result of a bite from an infected cat. It is noteworthy that cats who are found to harbor the organism in their oropharynx do not necessarily show signs of sickness.[2]

The function of the liver in removing pathogenic organisms from the portal blood is well known.[3] The presence of cirrhosis of the liver and a splenorenal shunt in this patient might be expected to facilitate the entry of pathogenic organisms into the systemic circulation. However, although the alimentary tract cannot be excluded as a portal of entry (the patient was in the habit of permitting her pet cat to lick her mouth and face), it seems more probable that the organism entered the body through the skin. The numerous healed scratch marks that were visible on the patient's skin were in favor of this hypothesis.

The case reported above appears to represent another case of infection by P. multocida caused by the bite of a domestic cat which, despite the isolation of virulent P. multocida organisms from the throat swabbings, appeared healthy. The prompt response of the patient to an injection of penicillin is in accord with the known susceptibility of P. multocida to penicillin.[4] Although aureomycin and terramycin[5] are also effective against this organism, streptomycin is known to be a relatively ineffective agent and hence the rapid response in this patient is almost certainly due to the administration of penicillin.

SUMMARY

A case of Pasteurella multocida septicemia in a patient with cirrhosis of the liver is described. An organism similar to that cultured from the blood of the patient was also isolated from the throat of the patient's pet cat.

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